JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim

Application Note

Pain-CKB, A Pain-Domain-Specific Chemogenomics Knowledgebase for Target Identification and Systems Pharmacology Research

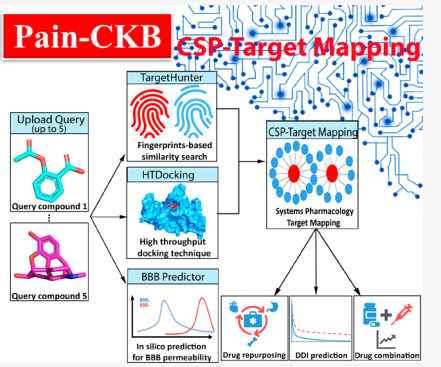
Zhiwei Feng,*,† Maozi Chen,† Mingzhe Shen, Tianjian Liang, Hui Chen, and Xiang-Qun Xie*

Cite This: https://dx.doi.org/10.1021/acs.jcim.0c00633

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A traditional single-target analgesic, though it may be highly selective and potent, may not be sufficient to mitigate pain. An alternative strategy for alleviation of pain is to seek simultaneous modulation at multiple nodes in the network of pain-signaling pathways through a multitarget analgesic or drug combinations. Here we present a comprehensive pain-domain-specific chemogenomics knowledgebase (Pain-CKB) with integrated computing tools for target identification and systems pharmacology research. Pain-CKB is constructed on the basis of our established chemogenomics technology with new features, including multiple compound support, multicavity protein support, and customizable symbol display. The determination of bioactivity is also revised to avoid the use of complex machine learning models. Our one-stop computing platform describes the chemical molecules, genes, and proteins involved in pain regulation. To date, Pain-CKB has archived 272 analgesics in the market, 84 pain-related targets with 207 available 3D crystal or cryo-EM structures, and 234 662 chemical agents reported for these target proteins. Moreover, Pain-CKB implements user-friendly web-interfaced computing tools and applications for the prediction and analysis of the relevant protein targets and visualization of the outputs, including HTDocking, TargetHunter, BBB permeation predictor, NGL viewer, Spider Plot, etc. The Pain-CKB server is accessible at https://www.cbligand.org/g/pain-ckb.



INTRODUCTION

Pain is an unpleasant sensation and distressing feeling that can sometimes affect a person's daily activity. Over 100 million adults in the United States suffer from chronic pain, which is more than the combined number of people who have diabetes, coronary heart disease, and cancer.[1] The causes of chronic pain are exceedingly diverse. For instance, aging affects both bones and joints, which may lead to chronic pain. Diseases such as multiple sclerosis, stomach ulcers, cancer, AIDS, arthritis, and gall bladder disease can also cause chronic pain.[2] To alleviate pain, many different groups of analgesics are on the market, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, acetylsalicylic acid, etc. Among these groups, opioids and NSAIDs are widely prescribed.

Opioids produce their pharmacological action by acting on receptors located on neuronal cell membranes. Though they are efficacious in relieving pain, the use of opiates can easily lead to drug abuse and addiction.[3] Federal government data show that in 2015, of the 20.5 million Americans 12 or older that had a substance use disorder (SUD), 2 million reported having a SUD associated with prescription pain relievers, and 591 000 reported having a SUD involving heroin. In 2017, the number of people in the United States suffering from SUDs remained significant, with an estimated 1.7 million suffering from SUDs related to prescription opioid pain relievers and 652 000 suffering from a heroin use disorder. That same year, more than 47 000 Americans died as a result of an opioid overdose, including prescription opioids, heroin, and illicitly manufactured fentanyl.[4] Besides the serious risks of addition and abuse, there are numerous side effects associated with the use of opioids, including sedation, constipation, tolerance, respiratory depression, etc. In comparison with opioids, NSAIDs are the mainstay for mild nociceptive pain, and they are safer to use in terms of addition. However, increased risks of gastrointestinal and cardiovascular complications are associated with NSAIDs. Other side effects such as heartburn, nausea, vomiting, and kidney damage are reported as well.[5] Analgesics available on the market can treat acute pain symptoms effectively, but they are less effectual for chronic pain and mostly ineffective for neuropathic pain.

Chronic or neuropathic pain involves simultaneous production of signals from a multitude of transduction pathways. Therefore, a traditional single-target analgesic may not be adequate to alleviate chronic pain, even though it may be highly selective and potent. An alternative strategy is to seek simultaneous modulation at multiple nodes in the network of

Received: June 5, 2020
Published: August 12, 2020

pain-signaling pathways through a multitarget analgesic[6] or drug combinations. There is now abundant evidence for this multitarget drug approach showing the beneficial effects on handling multifactorial diseases.[7]

In the present work, we developed an integrated pain-domain-specific chemogenomics knowledgebase, Pain-CKB, to facilitate pain research. Moreover, our established computational chemistry, chemoinformatics, and chemogenomics systems pharmacology-target (CSP-Target) mapping have been implemented into our chemogenomics database, which will help characterize pain-specific traits.

MATERIALS AND METHODS

Genes and Proteins. Genes and proteins related to pain or inflammation were collected from PubMed and other public resources, such as UniProt (https://www.uniprot.org/),[8] the Protein Data Bank (PDB) (https://www.rcsb.org/),[9] and the Therapeutic Target Database (TTD).[10−15] To date, we have collected 84 related targets with 207 available three-dimensional (3D) crystal or cryogenic electron microscopy (cryo-EM) structures that are associated with pain or inflammation.

Drugs and Chemicals. Using "pain" or "inflammation" as the keyword(s), we searched PubChem, the ChEMBL database (version 23),[16] and DrugBank database (version 5.1.5).[17] As a result, we retrieved 272 FDA-approved drugs (Table S1) and 234 662 related chemicals to be compiled into the Pain-CKB platform. These chemicals are related to the 84 pain targets (Table S2) in such a way that each chemical's bioactivity has been studied experimentally with one of the targets. Data collection and preparation used the same standard as described for our DAKB-GPCRs platform (https://www.cbligand.org/g/dakb-gpcrs).[18]

HTDocking. HTDocking,[19−23] an online high-throughput molecular docking technique used to identify the possible therapeutic targets for the user-query compound, is integrated into Pain-CKB. Depending on the availability of PDB files, up to three different structures (or conformations) with the highest resolutions for each pain-related protein were cleaned and collected in Pain-CKB. HTDocking, a program that started with the code base of the current stable version of idock (version 2.2.3),[24] automatically docks each query compound into the previously defined binding pockets of different structures (or conformations, up to three) and generates the respective docking scores. The higher the docking score, the more likely it is that the user-submitted compound will be the ligand of the target protein of interest.

TargetHunter. The second powerful web-interfaced tool integrated into Pain-CKB is called TargetHunter,[25] our online target-identification algorithm for predicting the therapeutic potential of the submitted compounds. For each query compound, TargetHunter calculates the similarity based on molecular fingerprints using the Tanimoto coefficients (from 0.0 for totally different to 1.0 for 100% similar) with each target protein's known active compound's data set collected from Drugs and Chemicals.

It is true that depending on the molecular fingerprints used, the coefficient can vary significantly. Indeed, our program supports up to 10 different kinds of molecular fingerprints, including FP2, ECFP6, ECFP4, MACCS, etc., as displayed on the job summary page. On the basis of the feedback and statistical data from our users, FP2 is the most popular and most accurate one. Thus, TargetHunter uses FP2 as the default fingerprint. In the future, we plan to allow users select the fingerprint used to perform their predictions.

Spider Plot. CSP-Target mapping or Spider Plot[18−20] is used to visualize the molecule−protein interaction network on the basis of the output of HTDocking and TargetHunter. Specifically, the similarity score from the TargetHunter protocol together with the docking results from HTDocking are used to determine the interactions. The actual algorithm depends on whether a target has known assay-proven active or inactive compounds. If a target has neither of such compounds or it has them but the most similar compound is weakly convincing (similarity score < 0.7), the interaction is solely determined by the docking results (active when the Vina metric is less than or equal to −8.5; user-customizable in the next release). Otherwise, the bioactivity state of the most similar compound is used.

The graphical user interface of Spider Plot was developed in the TypeScript language over the HTML5 canvas element, which allows fast dynamic rendering of 2D or 3D shapes and bitmap images. In plotting, the submitted compounds are presented as rounded rectangles labeled with the given compound name and the molecule depiction, while the predicted Pain-CKB targets are presented as circular discs labeled with the target symbol (either the protein symbol or gene symbol; user-customizable). The solid or dashed connection lines representing the predicted interactions are labeled with the average docking scores calculated from the docking scores for the conformations of a target. In case multiple binding cavities exist in a protein, the score of the cavity with the worst average score is plotted. By default, green target nodes connected with green solid lines represent the assay-proven targets of the compound(s) or high-potential targets having an assay-proven compound that is highly similar (similarity score ≥ 0.95) to the connecting submitted compound.

Blood−Brain Barrier (BBB) Permeation Predictor. Pain-CKB also implements our established machine-learning-based blood−brain barrier (BBB)[26,27] permeation predictor,[21−23] where the adaptive boost and support vector machine algorithms were applied. Recent studies[28,29] found that targeting only local inflamed tissue (while avoiding the brain) can lead to analgesic effects while avoiding the most dangerous side effects. Therefore, it is not always beneficial for an analgesic to permeate the BBB, as this can lead to side effects such as addiction. Therefore, our BBB permeation predictor may offer a way to find novel selective compounds.

Software Requirements. We recommend the latest release version of web browsers such as Chrome, Firefox, Microsoft Edge, and Safari for better rendering.

RESULTS AND DISCUSSION

Input. The Pain-CKB server is an integrated web server that combines our established tools and algorithms such as HTDocking,[19−23] TargetHunter,[25] BBB permeation predictor,[21−23] and Spider Plot,[18−20] as well as a few third-party software including Open Babel,[30] JSME Molecular Editor,[31] idock,[24] and NGL viewer[32] for target identification and network systems pharmacology analysis.

Figure S1 shows the user interfaces of Pain-CKB. Users can submit a query compound either by drawing its 2D structure with JSME Molecular Editor or by uploading a chemical file (SMILES/SDF) with the  button. A maximum of five compounds can be submitted together in one task using the Add Molecule button. Meaningful names for the job and each molecule are required. Clicking on the Create Job button will

https://dx.doi.org/10.1021/acs.jcim.0c00633
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

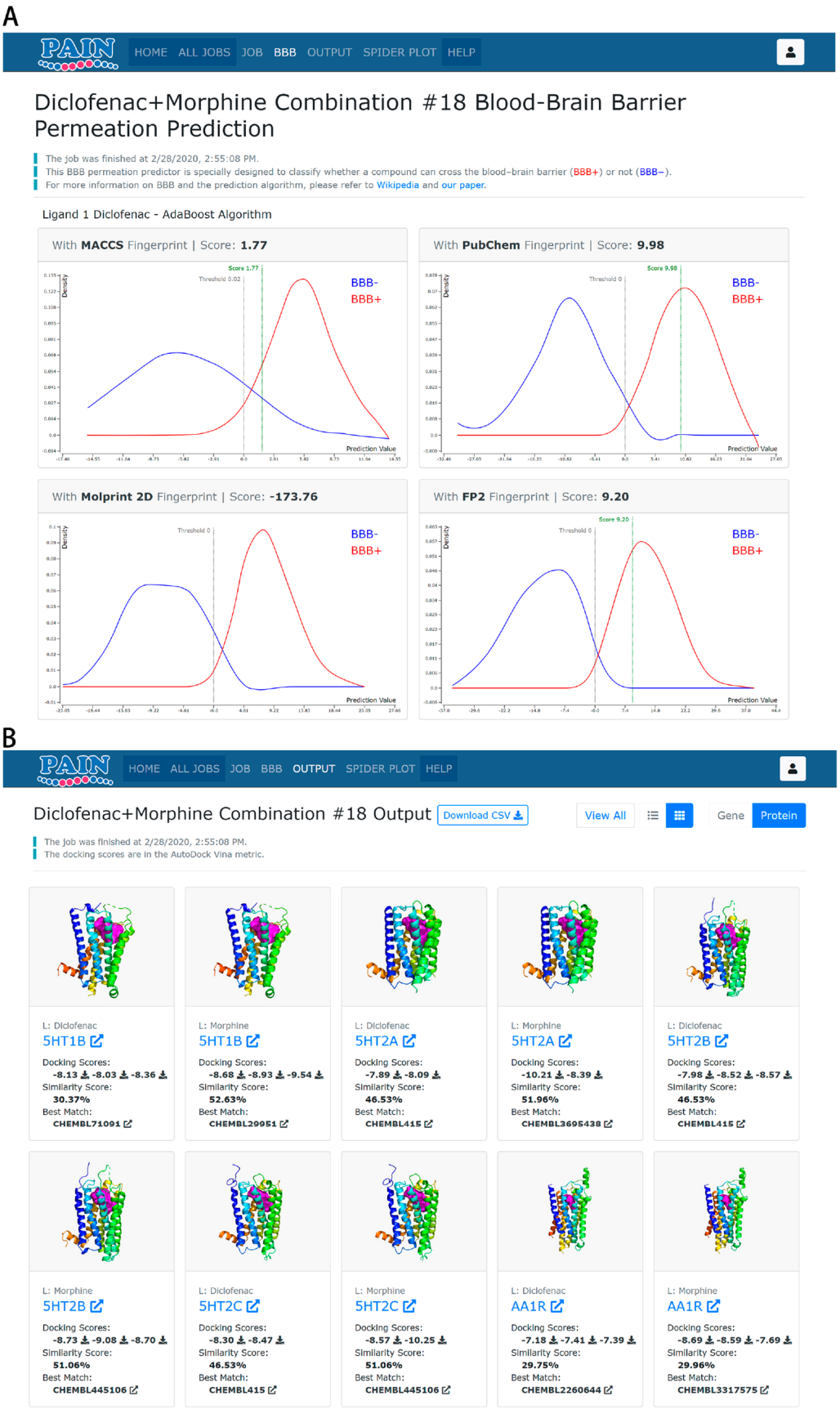


Figure 1. Output results of BBB permeation predictor, HTDocking, and TargetHunter in Pain-CKB. (A) Results from the BBB permeation predictor. (B) Results from HTDocking and TargetHunter in Tiled view manner. The displayed 3D structures are the first conformations of the targets if more than one exists. Clicking on the static 3D structure rendering displays the interactive one.

https://dx.doi.org/10.1021/acs.jcim.0c00633
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

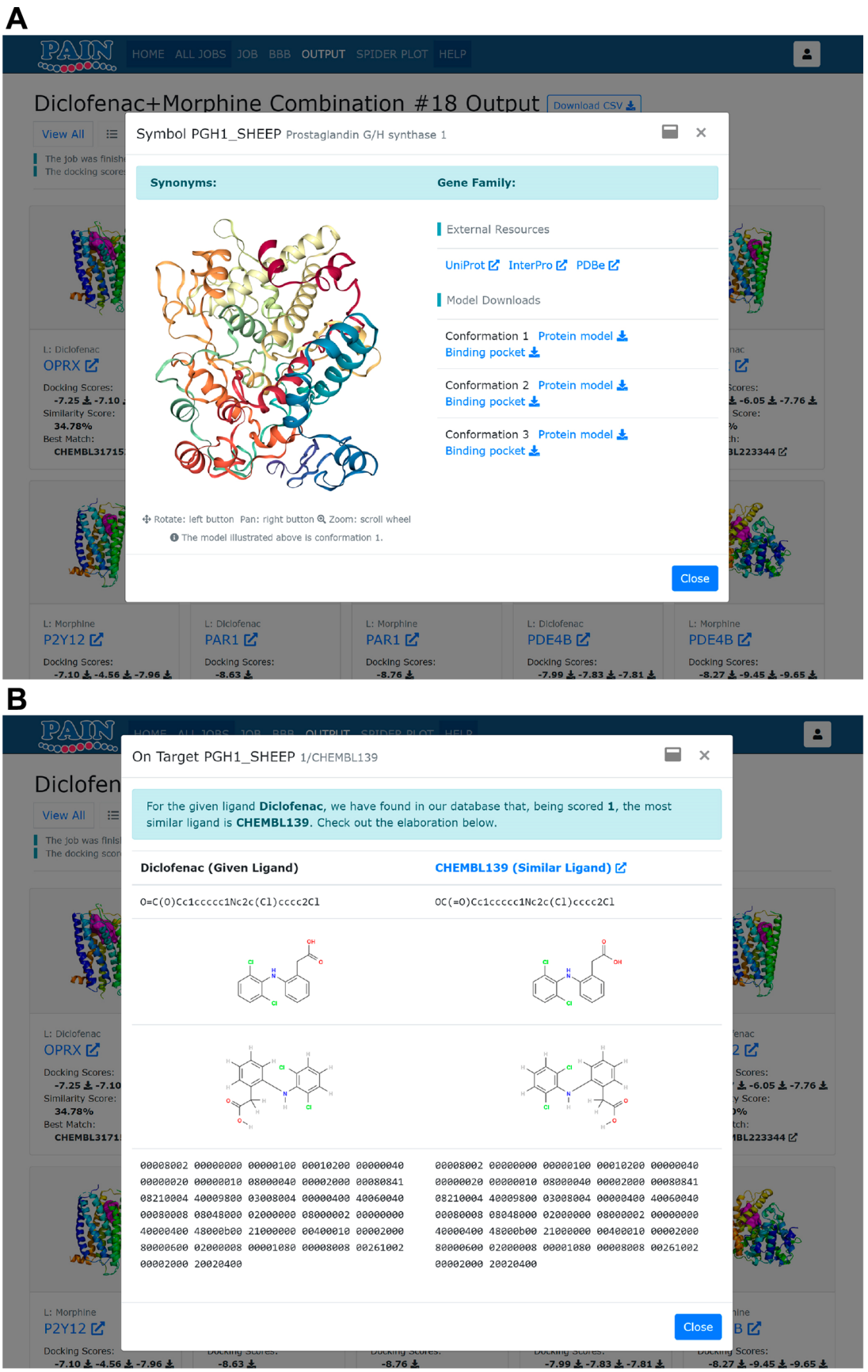


Figure 2. Information for a selected target and its best match compound in the data set. (A) Popup window presenting additional resources for a protein target. (B) Popup window showing the comparison between the query compound and the most similar compound in the data set.

https://dx.doi.org/10.1021/acs.jcim.0c00633
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

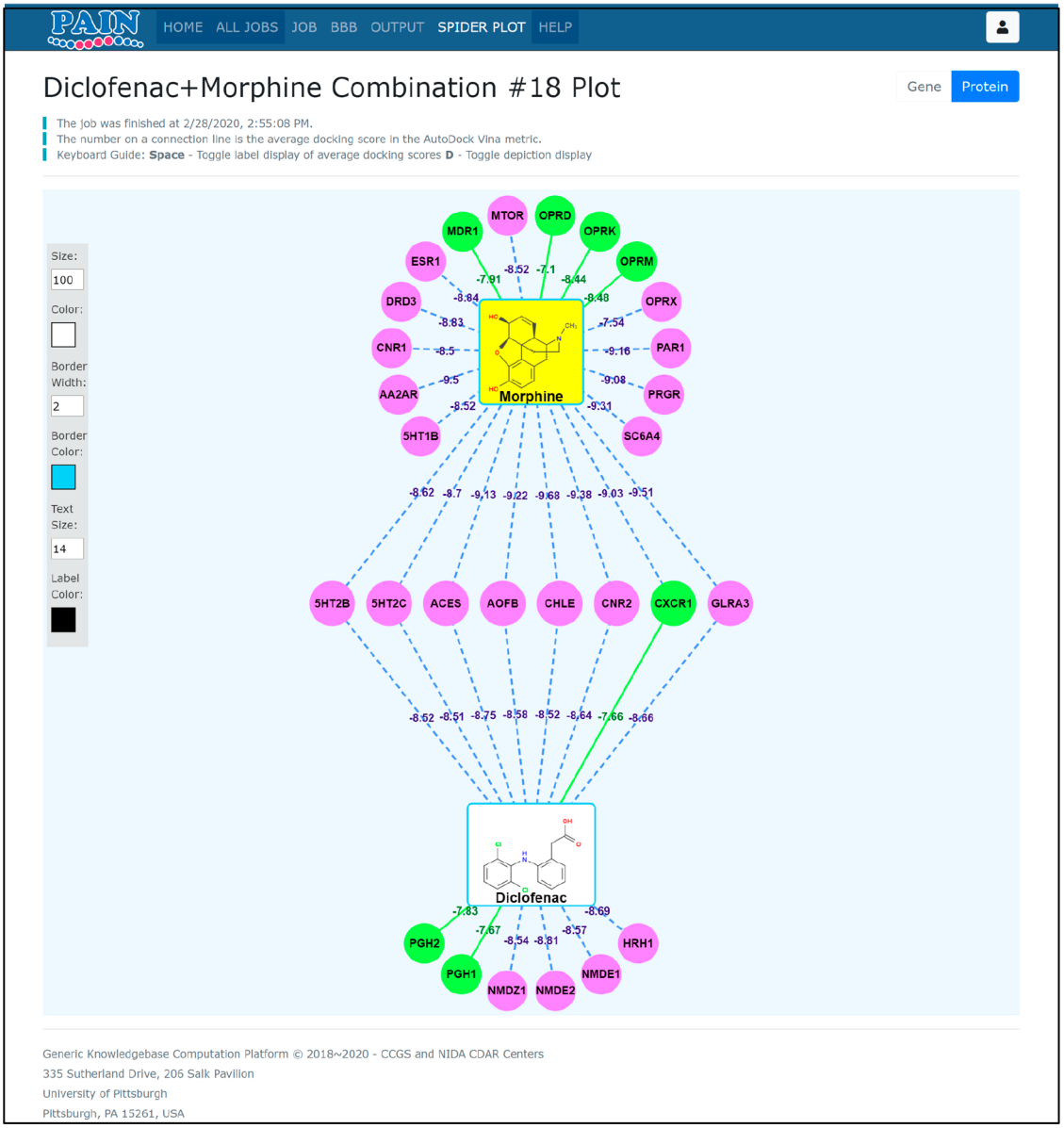


Figure 3. Spider Plot for data visualization and analysis. The average docking scores are displayed as connection labels, and the protein targets on which the query compound is active are displayed as circular discs.

initiate a new task. Afterward, a background job worker who periodically monitors the task queue will start to allocate computation resources and dispatch the computation task.

Output. As shown in Figure 1, the four buttons JOB, BBB, OUTPUT, and SPIDER PLOT are inserted between the HOME (Figure S2) and HELP (Figure S3) buttons on the menu bar when a specific job (Figure S4) is selected and accessed from the job listing page. Clicking on the BBB button takes the user to the output page of the BBB permeation predictor (Figure 1A), which displays the BBB permeation predictions of eight algorithm−fingerprint combinations for each submitted compound. Clicking on the OUTPUT button takes the user to the output page of the computation (Figure 1B), which is automatically updated with the most recent computed results in a real-time manner while the job is running. On the output page, each card includes docking scores computed against the conformations of the protein target using HTDocking and a similarity score calculated by TargetHunter (Figure 1B). Clicking on the SPIDER PLOT button shows the user an interactive vector-based graphic that visually demonstrates the predicted interaction network between the submitted compounds and the Pain-CKB targets (see below). The display name of the targets is customizable in both the text-based and graphic-based output pages simply by clicking on the "Gene/Protein" button group in the top right corner below the menu bar. Moreover, Pain-CKB provides the functionality of inspecting the target and interacting with the 3D protein structures (Figure 2A) via the button, downloading resulting docked conformations of the compounds via the button, and inspecting detailed information on the best-matched ChEMBL compounds (Figure 2B) via the button. To toggle between two views, the user can click on the iconic button group next to the "Gene/Protein" button group on the top right corner.

Case Study. We submitted diclofenac as the single query compound to our platform, and the results can be found in Figure S5. Our results showed that three green target nodes,

https://dx.doi.org/10.1021/acs.jcim.0c00633
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX

including C-X-C motif chemokine receptor 1 (CXCR1), prostaglandin G/H synthase 1 (PGH1), and prostaglandin G/H synthase 2 (PGH2), are connected to diclofenac with green solid lines, which is supported by the fact that diclofenac can bind to these receptors with high affinity. As we know, all three receptors are involved in the signaling pathway of inflammation or pain. That is, diclofenac can act on several targets simultaneously for the treatment of pain.

As shown in Figure 3, we then used morphine and diclofenac as the query compounds for further illustration. We observed that four green target nodes, including opioid receptor kappa 1 (OPRK), mu-type opioid receptor (OPRM), ATP binding cassette subfamily B member 1 (MDR1), and opioid receptor delta 1 (OPRD), are connected to morphine with green solid lines, which is consistent with the fact that morphine shows high activity at these four receptors. All of these results further validated that our algorithms are reliable. Moreover, our results showed that morphine predictively interacts with 14 targets. These 14 target nodes are placed in an arc without blocking connection lines for the common target nodes between morphine and diclofenac because the layout engine earned the knowledge about the space taken by them and adjust accordingly. Certainly, in silico predictions require in vitro target validation experiments as well as human clinical studies, which can help us improve the accuracy of our algorithms.

Statistical Analysis. Five non-analgesic and five analgesic drugs were submitted into our platform for further analysis. The results for the five non-analgesic drugs, including omeprazole (acid reflux), miglitol (diabetes), metformin (diabetes), oseltamivir (antiviral), and metolazone (high blood pressure), are shown in Figure S6. Because of the flexibility of omeprazole and metolazone, they were predicted to connect to many nodes. However, none of these nodes were highlighted with green color and solid lines, indicating these two drugs have not been proved to bind to pain-related targets. Moreover, no targets were connected to miglitol, metformin, and oseltamivir.

Figure S7 shows the predicted results for the five analgesic drugs, namely, oxycodone, diclofenac, dihydrocodeine, codeine, and morphine. Although some of these drugs are rigid with lower molecular weight, our results showed that all of them are connected to the known targets with green nodes and solid lines. In the future, we will try to develop or integrate more powerful algorithms into our platform to improve the accuracy.

CONCLUSIONS

In this study, we have provided a platform of national pain computing resources and tools to aid researchers in a broad range of disciplines and to help advance our knowledge about potential drug repurposing and drug combinations. We will integrate the information on gene signatures and signaling pathways of target proteins as well as our newly developed algorithms or tools into our Pain-CKB server in the future.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jcim.0c00633.

Figures S1−S7 and Tables S1 and S2 (PDF)

AUTHOR INFORMATION

Corresponding Authors

Xiang-Qun Xie − *Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, School of Pharmacy; National Center of Excellence for Computational Drug Abuse Research; Drug Discovery Institute; and Departments of Computational Biology and Structural Biology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States;* orcid.org/0000-0002-6881-6175; Email: xix15@pitt.edu

Zhiwei Feng − *Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, School of Pharmacy; National Center of Excellence for Computational Drug Abuse Research; Drug Discovery Institute; and Departments of Computational Biology and Structural Biology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States;* orcid.org/0000-0001-6533-8932; Email: zhf11@pitt.edu

Authors

Maozi Chen − *Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, School of Pharmacy; National Center of Excellence for Computational Drug Abuse Research; Drug Discovery Institute; and Departments of Computational Biology and Structural Biology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States*

Mingzhe Shen − *Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, School of Pharmacy; National Center of Excellence for Computational Drug Abuse Research; Drug Discovery Institute; and Departments of Computational Biology and Structural Biology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States*

Tianjian Liang − *Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, School of Pharmacy; National Center of Excellence for Computational Drug Abuse Research; Drug Discovery Institute; and Departments of Computational Biology and Structural Biology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States*

Hui Chen − *Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, School of Pharmacy; National Center of Excellence for Computational Drug Abuse Research; Drug Discovery Institute; and Departments of Computational Biology and Structural Biology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jcim.0c00633

Author Contributions

†Z.F. and M.C. contributed equally to this work.

Funding

The authors acknowledge funding support to the Xie laboratory from the National Institutes of Health, National Institute on Drug Abuse (P30 DA035778A1).

Notes

The authors declare no competing financial interest.

The Pain-CKB server is accessible at https://www.cbligand.org/g/pain-ckb.

REFERENCES

(1) Steglitz, J.; Buscemi, J.; Ferguson, M. J. The future of pain research, education, and treatment: a summary of the IOM report "Relieving pain in America: a blueprint for transforming prevention, care, education, and research". *Transl. Behav. Med.* **2012**, *2*, 6−8.

(2) Sachs-Ericsson, N.; Kendall-Tackett, K.; Hernandez, A. Childhood abuse, chronic pain, and depression in the National Comorbidity Survey. *Child Abuse Neglect* **2007**, *31*, 531−547.

(3) Kolodny, A.; Courtwright, D. T.; Hwang, C. S.; Kreiner, P.; Eadie, J. L.; Clark, T. W.; Alexander, G. C. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu. Rev. Public Health* **2015**, *36*, 559−574.

(4) *National Vital Statistics System: Mortality Statistics*. National Center for Health Statistics, Centers for Disease Prevention and Control, 2018. https://www.cdc.gov/nchs/nvss/deaths.htm (accessed 2020-06-05).

(5) Sostres, C.; Gargallo, C. J.; Arroyo, M. T.; Lanas, A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract. Res. Clin. Gastroenterol.* **2010**, *24*, 121−132.

(6) Lee, H.; Ahn, S.; Ann, J.; Ha, H.; Yoo, Y. D.; Kim, Y. H.; Hwang, J.-Y.; Hur, K.-H.; Jang, C.-G.; Pearce, L. V.; Esch, T. E.; Lewin, N. E.; Blumberg, P. M.; Lee, J. Discovery of dual-acting opioid ligand and TRPV1 antagonists as novel therapeutic agents for pain. *Eur. J. Med. Chem.* **2019**, *182*, 111634.

(7) Pang, M.-H.; Kim, Y.; Jung, K. W.; Cho, S.; Lee, D. H. A series of case studies: practical methodology for identifying antinociceptive multi-target drugs. *Drug Discovery Today* **2012**, *17*, 425−434.

(8) UniProt Consortium. UniProt: the universal protein knowledgebase. *Nucleic Acids Res.* **2017**, *45*, D158−D169, DOI: 10.1093/nar/gkw1099.

(9) Burley, S. K.; Berman, H. M.; Bhikadiya, C.; Bi, C.; Chen, L.; Di Costanzo, L.; Christie, C.; Dalenberg, K.; Duarte, J. M.; Dutta, S.; Feng, Z.; Ghosh, S.; Goodsell, D. S.; Green, R. K.; Guranovic, V.; Guzenko, D.; Hudson, B. P.; Kalro, T.; Liang, Y.; Lowe, R.; Namkoong, H.; Peisach, E.; Periskova, I.; Prlic, A.; Randle, C.; Rose, A.; Rose, P.; Sala, R.; Sekharan, M.; Shao, C.; Tan, L.; Tao, Y.-P.; Valasatava, Y.; Voigt, M.; Westbrook, J.; Woo, J.; Yang, H.; Young, J.; Zhuravleva, M.; Zardecki, C. RCSB Protein Data Bank: biological macromolecular structures enabling research and education in fundamental biology, biomedicine, biotechnology and energy. *Nucleic Acids Res.* **2019**, *47*, D464−D474.

(10) Li, Y. H.; Yu, C. Y.; Li, X. X.; Zhang, P.; Tang, J.; Yang, Q.; Fu, T.; Zhang, X.; Cui, X.; Tu, G.; Zhang, Y.; Li, S.; Yang, F.; Sun, Q.; Qin, C.; Zeng, X.; Chen, Z.; Chen, Y. Z.; Zhu, F. Therapeutic target database update 2018: enriched resource for facilitating bench-to-clinic research of targeted therapeutics. *Nucleic Acids Res.* **2018**, *46*, D1121−D1127.

(11) Qin, C.; Zhang, C.; Zhu, F.; Xu, F.; Chen, S. Y.; Zhang, P.; Li, Y. H.; Yang, S. Y.; Wei, Y. Q.; Tao, L.; Chen, Y. Z. Therapeutic target database update 2014: a resource for targeted therapeutics. *Nucleic Acids Res.* **2014**, *42*, D1118−D1123.

(12) Wang, Y.; Zhang, S.; Li, F.; Zhou, Y.; Zhang, Y.; Wang, Z.; Zhang, R.; Zhu, J.; Ren, Y.; Tan, Y.; Qin, C.; Li, Y.; Li, X.; Chen, Y.; Zhu, F. Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Res.* **2020**, *48*, D1031−D1041.

(13) Yang, H.; Qin, C.; Li, Y. H.; Tao, L.; Zhou, J.; Yu, C. Y.; Xu, F.; Chen, Z.; Zhu, F.; Chen, Y. Z. Therapeutic target database update 2016: enriched resource for bench to clinical drug target and targeted pathway information. *Nucleic Acids Res.* **2016**, *44*, D1069−D1074.

(14) Zhu, F.; Han, B.; Kumar, P.; Liu, X.; Ma, X.; Wei, X.; Huang, L.; Guo, Y.; Han, L.; Zheng, C.; Chen, Y. Update of TTD: Therapeutic Target Database. *Nucleic Acids Res.* **2010**, *38*, D787−D791.

(15) Zhu, F.; Shi, Z.; Qin, C.; Tao, L.; Liu, X.; Xu, F.; Zhang, L.; Song, Y.; Liu, X.; Zhang, J.; Han, B.; Zhang, P.; Chen, Y. Therapeutic target database update 2012: a resource for facilitating target-oriented drug discovery. *Nucleic Acids Res.* **2012**, *40*, D1128−36.

(16) Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; Overington, J. P. ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* **2012**, *40*, D1100−D1107.

(17) Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; Maciejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, D.; Pon, A.; Knox, C.; Wilson, M. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.* **2018**, *46*, D1074−D1082.

(18) Chen, M.; Jing, Y.; Wang, L.; Feng, Z.; Xie, X.-Q. DAKB-GPCRs: An Integrated Computational Platform for Drug Abuse Related GPCRs. *J. Chem. Inf. Model.* **2019**, *59*, 1283−1289.

(19) Cheng, J.; Wang, S.; Lin, W.; Wu, N.; Wang, Y.; Chen, M.; Xie, X.-Q.; Feng, Z. Computational Systems Pharmacology-Target Mapping for Fentanyl-Laced Cocaine Overdose. *ACS Chem. Neurosci.* **2019**, *10*, 3486−3499.

(20) Chen, Y.; Feng, Z.; Shen, M.; Lin, W.; Wang, Y.; Wang, S.; Li, C.; Wang, S.; Chen, M.; Shan, W.; Xie, X.-Q. Insight into Ginkgo biloba L. Extract on the Improved Spatial Learning and Memory by Chemogenomics Knowledgebase, Molecular Docking, Molecular Dynamics Simulation, and Bioassay Validations. *ACS Omega* **2020**, *5*, 2428−2439.

(21) Liu, H.; Wang, L.; Lv, M.; Pei, R.; Li, P.; Pei, Z.; Wang, Y.; Su, W.; Xie, X.-Q. AlzPlatform: an Alzheimer's disease domain-specific chemogenomics knowledgebase for polypharmacology and target identification research. *J. Chem. Inf. Model.* **2014**, *54*, 1050−1060.

(22) Chen, M.; Jing, Y.; Wang, L.; Feng, Z.; Xie, X. Q. DAKB-GPCRs: An Integrated Computational Platform for Drug Abuse Related GPCRs. *J. Chem. Inf. Model.* **2019**, *59* (4), 1283−1289.

(23) Feng, Z.; Chen, M.; Liang, T.; Shen, M.; Chen, H.; Xie, X. Q. Virus-CKB: an integrated bioinformatics platform and analysis resource for COVID-19 research. *Briefings Bioinf.* **2020**, bbaa155.

(24) Li, H.; Leung, K.-S.; Ballester, P. J.; Wong, M.-H. istar: a web platform for large-scale protein−ligand docking. *PLoS One* **2014**, *9*, e85678.

(25) Wang, L.; Ma, C.; Wipf, P.; Liu, H.; Su, W.; Xie, X.-Q. TargetHunter: an in silico target identification tool for predicting therapeutic potential of small organic molecules based on chemogenomic database. *AAPS J.* **2013**, *15*, 395−406.

(26) Ma, C.; Wang, L.; Xie, X.-Q. Ligand Classifier of Adaptively Boosting Ensemble Decision Stumps (LiCABEDS) and its application on modeling ligand functionality for 5HT-subtype GPCR families. *J. Chem. Inf. Model.* **2011**, *51*, 521−531.

(27) Ma, C.; Wang, L.; Yang, P.; Myint, K. Z.; Xie, X.-Q. LiCABEDS II. Modeling of ligand selectivity for G-protein-coupled cannabinoid receptors. *J. Chem. Inf. Model.* **2013**, *53*, 11−26.

(28) Lešnik, S.; Hodošček, M.; Bren, U.; Stein, C.; Bondar, A.-N. Potential Energy Function for Fentanyl-Based Opioid Pain Killers. *J. Chem. Inf. Model.* **2020**, *60*, 3566−3576.

(29) Spahn, V.; Del Vecchio, G.; Labuz, D.; Rodriguez-Gaztelumendi, A.; Massaly, N.; Temp, J.; Durmaz, V.; Sabri, P.; Reidelbach, M.; Machelska, H.; Weber, M.; Stein, C. A nontoxic pain killer designed by modeling of pathological receptor conformations. *Science* **2017**, *355*, 966−969.

(30) O'Boyle, N. M.; Banck, M.; James, C. A.; Morley, C.; Vandermeersch, T.; Hutchison, G. R. Open Babel: An open chemical toolbox. *J. Cheminf.* **2011**, *3*, 33.

(31) Ertl, P. Molecular structure input on the web. *J. Cheminf.* **2010**, *2*, 1.

(32) Rose, A. S.; Bradley, A. R.; Valasatava, Y.; Duarte, J. M.; Prlic, A.; Rose, P. W. NGL viewer: web-based molecular graphics for large complexes. *Bioinformatics* **2018**, *34*, 3755−3758.

https://dx.doi.org/10.1021/acs.jcim.0c00633
J. Chem. Inf. Model. XXXX, XXX, XXX−XXX