


Systems biology

DREIMT: a drug repositioning database and prioritization tool for immunomodulation

Kevin Troulé^{1,†}, Hugo López-Fernández^{2,3,†}, Santiago García-Martín¹, Miguel Reboiro-Jato^{2,3}, Carlos Carretero-Puche¹, Jordi Martorell-Marugán⁴, Guillermo Martín-Serrano¹, Pedro Carmona-Sáez⁴, Daniel Glez-Peña^{2,3}, Fátima Al-Shahrour ^{1,*} and Gonzalo Gómez-López^{1,*}

¹Bioinformatics Unit, Structural Biology Department, Spanish National Cancer Research Centre (CNIO), Madrid 28029, Spain, ²SING Research Group, Biomedical Research Centre (CINBIO), E-36310, Vigo, Spain, ³ESEI - Escuela Superior de Ingeniería Informática, Department of Computer Science, Universidad de Vigo, E-32004, Ourense, Spain and ⁴Bioinformatics Unit, GENYO, Centre for Genomics and Oncological Research, Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, E-18016 Granada, Spain

*To whom correspondence should be addressed.

[†]The authors wish it to be known that, in their opinion, the first two authors should be regarded as Joint First Authors.

Associate Editor: Pier Luigi Martelli

Received on June 2, 2020; revised on July 22, 2020; editorial decision on August 7, 2020; accepted on August 16, 2019

Abstract

Motivation: Drug immunomodulation modifies the response of the immune system and can be therapeutically exploited in pathologies such as cancer and autoimmune diseases.

Results: DREIMT is a new hypothesis-generation web tool, which performs drug prioritization analysis for immunomodulation. DREIMT provides significant immunomodulatory drugs targeting up to 70 immune cells subtypes through a curated database that integrates 4960 drug profiles and ~2600 immune gene expression signatures. The tool also suggests potential immunomodulatory drugs targeting user-supplied gene expression signatures. Final output includes drug–signature association scores, FDRs and downloadable plots and results tables.

Availability and implementation: <http://www.dreimt.org>.

Contact: falshahrour@cnio.es or ggomez@cnio.es

Supplementary information: [Supplementary data](#) are available at *Bioinformatics* online.

1 Introduction

Immune system dysregulations have been related to a wide spectrum of complex diseases such as autoimmune disorders and cancer. Autoimmunity processes are clinically diverse, and they are distinguished by an immune-mediated attack on the body's own tissues led by self-reactive B and T cells (Rose, 2016). In cancer, the intercellular signaling between the malignant cells and certain immune-cell subpopulations [e.g. regulatory T cells (Tregs) and tumor-associated macrophages (TAMs)] contributes to tumor microenvironment immunosuppression fostering cell proliferation and tumor evasion (Linde *et al.*, 2018; Stockis *et al.*, 2019). The presence of Tregs and TAMs subpopulations in tumor microenvironment has been also correlated with cancer poor prognosis in contrast to better prognosis shown by those tumors with high rate of tumor-infiltrated CD8⁺ T cells (Fridman *et al.*, 2017). This has led to propose immune cells targeting as a therapeutic strategy. For instance, some studies have shown that activity of specific immune cell populations can be targeted using systemic or non-systemic

approaches (e.g. drug-conjugated nanoparticles) thus enhancing the outcome of some tumors and autoimmune diseases (Genovese *et al.*, 2016; Lu *et al.*, 2020; Riley *et al.*, 2019). Recently, drug-mediated immunomodulation has been proposed as a therapeutic approach in patients with COVID-19 associated cytokine storm (Richardson *et al.*, 2020). This highlights the interest in developing new methodologies to propose immunomodulatory therapeutic strategies capable of selectively affect the function of specific immune cells. Here, we introduce Drug REpositioning for IMMune Transcriptome (DREIMT), a tool for hypothesis generation of drugs capable of modulating (boosting or inhibiting) the immune cells activity.

2 Methods and features

DREIMT integrates ~2.6k immune gene expression signatures with a collection of 4690 consensus drug profiles (Perales-Patón *et al.*, 2019) from the catalog of drug perturbations expression profiles in cancer cell lines from the LINCS L1000 dataset (Subramanian *et al.*,

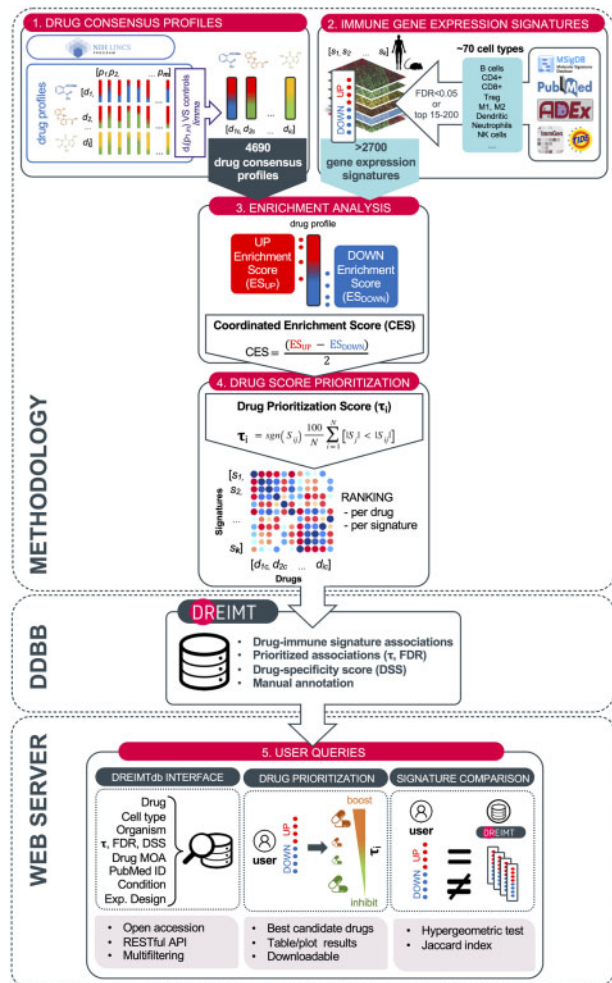


Fig. 1. DREIMT workflow

2017) (Fig. 1). Immune signatures were obtained from published studies and public databases covering up to 70 immune cell subtypes (Supplementary Materials S1–S3, T1). DREIMT performs an fgsea to test the significance of the immune signature enrichment across the ranked genes of each drug profile (Korotkevich *et al.*, 2019). The fgsea enrichment scores are used to calculate the Drug Prioritization score (τ), as described elsewhere (Subramanian *et al.*, 2017), comparing the obtained enrichment score for a particular signature to the rest of immune signatures. The τ score allows the prioritization of drugs to target immune cells. DREIMT also includes a Drug Specificity Score (DSS) that summarizes the cell-specificity of a given drug across multiple cancer cell lines (Hodos *et al.*, 2018; Supplementary Materials S4–S6). Significant drug–immune signature associations ($|\tau| > 80$) are stored in the DREIMT database (DREIMTdb) accessible through a RESTful API. We have validated >20 DREIMT hypothesis by scientific literature (Supplementary Materials S10, T2).

3 Dreimt web server

DREIMT web server functionalities include DREIMTdb interface, drug prioritization and signature comparison tools (Fig. 1). DREIMTdb interface allows an easy interrogation of the drug–immune signature associations allowing multifiltering for advanced queries. Drug prioritization functionality allows the search for the

best candidate drugs to boost or inhibit the user-defined immune gene expression signature of interest. Drug results are prioritized by τ and DSS and filtered by statistical significance (FDR < 0.05). Final outputs are displayed as fully downloadable tables and plots. In addition, users can compare their own gene signatures against full DREIMTdb contents. As a result, the tool provides the similarity score (jaccard index) and FDR value per each signature compared (Supplementary Materials S8 and S9). Implementation details and links to the source code repositories, are provided in the Supplementary Materials S11.

4 Conclusions

Drugs affect the biology and activity of the immune system; however, such interactions are often poorly understood. We have developed DREIMT, a tool to allow users to generate hypotheses and explore novel druggable targets across the immune system, thus supporting drug repositioning leveraging transcriptomics data. DREIMT is fully accessible at <http://www.dreimt.org>.

Acknowledgements

José Antonio López for the fruitful discussions for the development of the DREIMT concept. B.U. staff for beta testing and DREIMTdb curation.

Funding

CNIO Bioinformatics Unit staff was supported by the Instituto de Salud Carlos III (ISCIII); Spanish National Bioinformatics Institute (PT17/0009/0011 – ISCIII-SGEFI/ERDF); RETOS (RTI2018-097596-B-I00); Paradifference Foundation. K.T. was supported by Severo Ochoa FPI; S.G.-M. was supported by Comunidad de Madrid [PEJD-2019-PRE/BMD-15732]. H.L.-F. is supported by C. de Educación, Universidades e Formación Profesional (Xunta de Galicia); ED431C2018/55-GRC Competitive Reference Group. P.C.-S. was supported by Junta de Andalucía [PI-0173-2017].

Conflict of Interest: none declared.

References

- Fang, R.H. and Zhang, L. (2016) Nanoparticle-based modulation of the immune system. *Annu. Rev. Chem. Biomol. Eng.*, **7**, 305–326.
- Fridman, W.H. *et al.* (2017) The immune contexture in cancer prognosis and treatment. *Nat. Rev. Clin. Oncol.*, **14**, 717–734.
- Genovese, M.C. *et al.* (2016) Baricitinib in patients with refractory rheumatoid arthritis. *N. Engl. J. Med.*, **374**, 1243–1252.
- Hodos, H. *et al.* (2018) Cell-specific prediction and application of drug-induced gene expression profiles. *Pac. Symp. Biocomput.*, **23**, 32–43.
- Korotkevich, G. *et al.* (2019) Fast gene set enrichment analysis. *bioRxiv* 060012; doi:10.1101/060012.
- Linde, N. *et al.* (2018) Macrophages orchestrate breast cancer early dissemination and metastasis. *Nat. Commun.*, **9**, 21.
- Lu, Y. *et al.* (2020) Complement signals determine opposite effects of B cells in chemotherapy-induced immunity. *Cell*, **180**, 1081–1097.
- Perales-Patón, J. *et al.* (2019) vulcanSpot: a tool to prioritize therapeutic vulnerabilities in cancer. *Bioinformatics*, **35**, 4846–4848.
- Richardson, P. *et al.* (2020) Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*, **395**, e30–e31.
- Riley, R.S. *et al.* (2019) Delivery technologies for cancer immunotherapy. *Nat. Rev. Drug Discov.*, **18**, 175–196.
- Rose, N.R. (2016) Prediction and prevention of autoimmune disease in the 21st Century: a review and preview. *Am. J. Epidemiol.*, **183**, 403–406.
- Stockis, J. *et al.* (2019) Regulation of regulatory T cells in cancer. *Immunology*, **157**, 219–231.
- Subramanian, A. *et al.* (2017) A next generation connectivity map: 1 000 platform and the first 1,000,000 profiles. *Cell*, **171**, 1437–1452.