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DREIMT: a drug repositioning database and prioritization tool for immunomodulation

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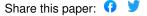
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DREIMT: repositioning prioritization а drug database and tool for immunomodulation.

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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 immunomodulation. DREIMT provides significant for

immunomodulatory drugs targeting up to 70 immune cells subtypes through a curated

database that integrates 4,960 drug profiles and ~2,6K 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: http://www.dreimt.org

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

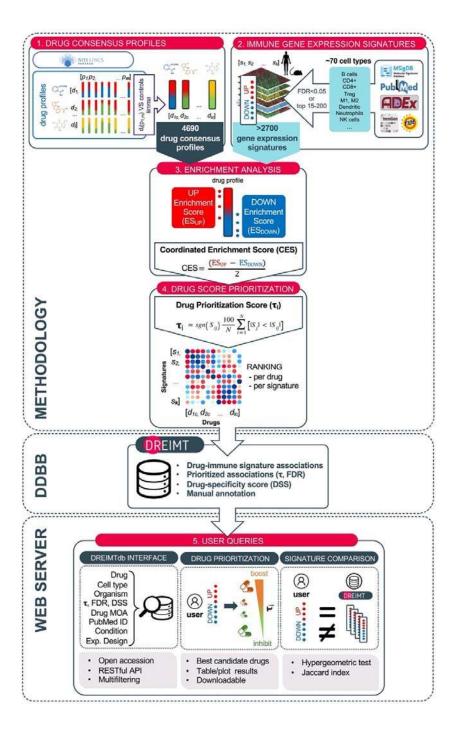
1 Introduction

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 et al. 2016). In cancer, the intercellular signalling 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 (Stockis et al. 2019; Linde et al. 2018). 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. drugconjugated nanoparticles) thus enhancing the outcome of some tumors and autoimmune diseases (Lu et al. 2020; Riley et al., 2019; Genovese et al., 2016). Recently, drugmediated immunomodulation has been proposed as a therapeutic approach in patients with COVID-19 associated cytokine storm (Richardson P 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 DREIMT (Drug REpositioning for IMmune Transcriptome), 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.*, 2017) (Figure 1). Immune signatures were obtained from published studies and public databases covering up to 70 immune cell subtypes (Suppl. Materials S1-3, T1). DREIMT performs a fgsea to test the significance of the immune signature enrichment across the ranked genes of each drug profile (Korotkevich *et al.*, 2020). The fgsea enrichment scores are used to calculate the Drug Prioritization score (T) as described elsewhere (Subramanian et al., 2017), comparing the obtained enrichment score for a particular signature to the rest of immune signatures. The T score allows the prioritization of drugs to target immune cells. DREIMT also includes a Drug Specificity Score (DSS) that summarises the cell-specificity of a given drug across multiple cancer cell lines (Hodos *et al.*, 2018; Suppl. Materials S4-6). Significant drug-immune signature associations (|T|>80) are stored in the DREIMT database (DREIMTdb) accessible through a RESTful API. We have validated >20 DREIMT hypothesis by scientific literature (Suppl. Materials S7, T2).

Fig. 1. DREIMT workflow.



3 DREIMT web server

DREIMT web server functionalities include DREIMTdb interface, drug prioritization and signature comparison tools (Figure 1). DREIMTdb interface allows an easy interrogation of the drug-immune signature associations allowing multi-filtering 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. Additionally, 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 (Suppl. Materials S8,9). Implementation details and links to the source code repositories, are provided in the Suppl. Materials S10.

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.

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Conflict of Interest: none declared.

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1. DRUG CONSENSUS PROFILES 2. IMMUNE GENE EXPRESSION SIGNATURES ~70 cell types NIH LINCS $[S_{1_i} S_2]$ B cells ... **p**_m] CD4+ CD8+ Publied $[d_{1,}]$ FDR<0.05 Treg M1, M2 • • • • • • top 15-200 Dendritic Neutrophils $[d_{1c}, d_{2c}]$ ImmGen NK cells 4690 >2700 ... gene expression drug consensus profiles signatures 3. ENRICHMENT ANALYSIS drug profile DOWN Enrichment Enrichment Score (ES_{UP}) Score Coordinated Enrichment Score (CES) $(ES_{UP} - ES_{DOWN})$ CES = 4. DRUG SCORE PRIORITIZATION Drug Prioritization Score (τ_i) $\mathbf{\tau_i} = sgn(S_{ij}) \frac{100}{N} \sum_{i=1}^{N} [|S_j| < |S_{ij}|]$ RANKING per drug - per signature $[d_{1c}, d_{2c}, d_{ic}]$ Drugs DREIMT Drug-immune signature associations Prioritized associations (τ, FDR) Drug-specificity score (DSS) Manual annotation 5. USER QUERIES DREIMTdb INTERFACE SIGNATURE COMPARISON DRUG PRIORITIZATION Drug Cell type Organism user DREIMT FDR, DSS Drug MOA user PubMed ID Condition Exp. Design inhibit Open accession Best candidate drugs Hypergeometric test RESTful API Table/plot results Jaccard index Multifiltering Downloadable