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Targeting Monocyte Abnormalities in Systemic Lupus Erythematosus through Omics-Based Drug Repurposing

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Commentary

Systemic Lupus Erythematosus (SLE) is a complex disease marked by extensive immune system dysfunction, culminating in a diverse spectrum of clinical phenotypes of varying severity [1]. Despite the significant advancements in elucidating the pathogenesis of the disease, the management of SLE remains largely empirical with attainment of low disease activity and remission targets being an infrequent outcome among patients [1]. Strikingly, the intricate molecular landscape and the notorious heterogeneity of the disease pose substantial challenges in the design of successful clinical trials, resulting in the scarcity of approved therapeutic modalities, which further amplifies the burden on SLE patients.

The systemic nature of the disease underscores the widely distributed immune alterations that drive autoimmunity targeting nucleic acids and their associated proteins,

and inciting tissue-damaging inflammation [2]. Evidence highlights the essential role of innate immune system in the initiation, propagation of autoimmunity and development of organ damage in SLE [3] and a plethora of phenotypic and functional abnormalities of the macrophage/monocyte lineage cells has been reported [4,5]. The impaired phagocytic activity of macrophages resulting in the inefficient clearance of apoptotic material and immune-complexes is instrumental in the breakdown of self-tolerance and the subsequent promotion of autoantibody production, a unifying feature of SLE [6]. Additionally, in SLE, monocytes are acknowledged as significant contributors to the type I interferon production, a hallmark of the disease [7]. Monocytes serve as the primary source of IFN in the pristane-induced murine lupus model, defined by high IFN signature, and human monocyte-derived macrophages demonstrate elevated IFN-α and IFN-β gene expression when transfected with a small non-coding Y RNA or stimulated with immune complexes [7]. The aberrant activation of autoreactive B and T cells observed in SLE could be partially ascribed to the dysregulated cytokine production by monocytes. Monocytes from SLE patients exhibit heightened production of B-lymphocyte stimulator (BLyS), fostering the survival and proliferation of B cells [8]. Moreover, in the peripheral blood of SLE patients, monocytes are major producers of IL-10 and IL-6, amplifying antibody production and facilitating plasma cell differentiation, respectively [8]. Thus, directing therapeutic interventions towards monocytes could potentially target fundamental abnormalities in SLE, offering significant therapeutic benefits to the patients.

Considering the paucity of approved medications in SLE and the high attrition rates, repurposing "old" drugs for the disease is increasingly appealing, providing the advantage of utilizing de-risked compounds for new indications. Advanced computational tools have streamlined both *de novo* drug development and drug repurposing processes, enabling the reduction of overall costs and shortening development timelines (**Table 1**). The Connectivity Map (CMap) project serves as a pioneering drug repurposing platform, incorporating gene expression responses from four human cell lines exposed to various doses of a large collection of FDA-approved compounds [9]. Building upon this groundwork, the NIH-supported Library of Integrated Network-Based Cellular Signatures (LINCS) expanded the transcriptomic databases of the CMap project by integrating gene expression profiles from over 60 cell lines before and after exposure to more than 20,000 perturbagens [10]. Using the Lincscloud, the successor to CMap, drug candidates capable of reversing the SLE-related transcriptional signatures were determined, highlighting the therapeutic potential of phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitors in SLE therapeutics [11]. Utilizing CMap for computational drug repurposing analysis and integrating significant gene targets derived from transcriptome-wide association studies, several clinically relevant drug classes potentially suitable for SLE treatment were detected [12]. Among these are glucocorticoid receptor agonists, histone deacetylase (HDAC) inhibitors, mTOR inhibitors, and topoisomerase inhibitors, all identified as promising candidates [12]. In the same context, patient stratification based on the drug responsiveness suggested that mTOR and TNFa inhibitors could potentially reverse the transcriptional signatures of the lymphocyte- and neutrophil-driven subgroups, respectively [13]. Achieving low disease activity state or remission is crucial for SLE patients, offering

Table 1. Selected studies of computational drug repurposing in SLE.

Study (year of publication)	Computational approach	Key drug candidates
Toro-Domínguez et al. (2017) [11]	Lincscloud	PI3K and mTOR inhibitors
Toro-Domínguez et al. (2019) [13]	CLUE	mTOR and TNFa inhibitors
Owen et al. (2020) [25]	LINCS, STITCH (v.5.0), and IPA	African ancestry: bortezomib, PF-06650833, IRAK4-specific inhibitor; European ancestry: TYK2 inhibitor
Noor et al. (2021) [26]	Semantic Web (SW) technologies	Aspirin, azathioprine, cyclophosphamide, indomethacin, methotrexate, leflunomide, warfarin, clopidogrel, peginterferon alfa-2a, and peginterferon alfa-2b
Frangou et al. (2022) [16]	L1000 Characteristic Direction Signature Search Engine (L1000CDS2)	R(+)−6-BROMO-APB, HEMADO, norketamine hydrochloride and trichostatin A
Garantziotis et al. (2022) [17]	CMap, iLINCS	PI3K/mTOR pathway inhibitors, JAK2 inhibitor
Nikolakis et al. (2023) [19]	iLINCS, CLUE, L1000CDS2, DGIDb	NF-κB inhibitor, Pim-1/NFATc1/NLRP3 pathway inhibitor, HSP90 inhibitors
Khunsriraksakul et al. (2023) [12]	CMap	Glucocorticoid receptor agonist, HDAC inhibitor, mTOR inhibitor, and topoisomerase inhibitor
Parodis et al. (2024) [15]	Reactome Pathways	Bruton tyrosine kinase inhibitors, TLR7 and TLR9 inhibitors

significant benefits in terms of minimizing organ damage accrual and preventing flares [14]. Interestingly, the drug-target interaction analysis highlights the modulation of toll-like receptor (TLR) cascades, Bruton tyrosine kinase (BTK) activity, cytotoxic T lymphocyte antigen 4 (CTLA-4)-related inhibitory signaling, and the nucleotide-binding oligomerization domain leucine-rich repeat-containing protein 3 (NLRP3) inflammasome pathways as promising strategies for attaining lupus low disease activity state or remission in SLE [15].

Our group has also previously employed computational signature mapping, comparing transcriptional profiles of drugs against diseases or clinical phenotypes, to identify potential novel therapeutic agents in autoimmune diseases [16-19]. Applying an unbiased, whole blood transcriptome driven molecular taxonomy approach and leveraging two robust, high throughput platforms (iLINCS and CLUE), we devised a personalized drug repurposing pipeline to propose novel compounds capable of counteracting the endotype-specific transcriptional abberations observed in SLE patients [17]. Notably, agents such as dactolisib and fedratinib, targeting the PI3K/mTOR and the JAK/STAT pathways respectively, emerged as promising candidates to ameliorate the SLE related transcriptional disturbances in a personalized manner [17]. In light of the limitations of the currently available therapeutic interventions, failing to induce remission in over 50% of patients with lupus nephritis (LN), we next conducted a comparative cross-tissue and cross-species gene expression analysis to identify nephritis-specific genes for subsequent drug repurposing analysis [16]. Using the L1000 Characteristic Direction Signature Search Engine, we detected agents predicted to reverse the transcriptional signatures associated with active LN and the transition from preclinical to overt disease [16]. Among these, R(+)−6-BROMO-APB was predicted to reverse the former signature, while HEMADO, norketamine hydrochloride, and trichostatin A were anticipated to counteract the latter signature in the HA1E kidney cell line, indicating the potential for further evaluation in LN therapeutics [16].

Given the reasonable assumption that drugs reversing the transcriptional profile linked to a disease state hold therapeutic promise and acknowledging the pivotal involvement of macrophage/monocyte lineage cells in SLE pathogenesis, the identification of compounds capable of modifying SLE-specific transcriptional abnormalities in monocytes warrants significant consideration. Employing the iLINCS, CLUE, and L1000CDS2 platforms, we identified small molecules predicted to most effectively counteract the SLE monocyte-specific gene signature [19]. Compounds disrupting the Pim-1/NFATc1/NLRP3 signaling axis or inhibiting the heat shock protein 90 (HSP90) were forecasted to efficiently mitigate the abnormal monocyte signature in SLE, consistent with experimental evidence suggesting that inhibition of the Pim-1/NFATc1/NLRP3 pathway improves nephritis in lupus mouse models [20], and HSP90 facilitates TLR7/9-mediated nucleic acid recognition in SLE [21].

Focusing solely on transcriptome reversal may overlook opportunities to modulate key regulatory hub genes within the biological system, potentially constraining the effectiveness of drug repurposing endeavors. Therefore, adopting a holistic approach that integrates information on hub genes and their interactions alongside transcriptomic data is essential to ensure comprehensive target identification and therapeutic efficacy. Applying a network-based drug repurposing strategy incorporating upstream regulators of the SLE monocyte-signature, the IL-12/IL-23 inhibitor ustekinumab was identified as a potential candidate for efficiently disrupting the molecular interaction network of monocytes. While proteasome inhibitors effectively deplete autoreactive plasma cells and demonstrate therapeutic efficacy in preclinical mouse models of LN, evidence suggests that immunoproteasome inhibition may selectively induce apoptosis in CD14+ monocytes, supporting the validity of our network-based drug repurposing strategy, which implied the therapeutic targeting of SLE monocytes by bortezomib [22].

Despite the significant successes achieved in drug repurposing, several limitations must be carefully considered [23,24]. While repurposed drugs may bypass phase I clinical trials, which primarily focus on safety evaluation, concerns regarding drug safety remain a significant challenge. The safety profile established for a drug in one patient population may not automatically translate to another population, prompting a need for the re-evaluation of safety parameters. Furthermore, the dosing regimen validated for the original indication may not be optimal for new therapeutic uses, necessitating adjustments and further investigation. Lack of specificity for the new indication poses a substantial hurdle, particularly when utilizing SLE blood specimens that do not entirely mirror the molecular alterations in target tissues. Lastly, intellectual property barriers can impose additional limitations on the drug repurposing process.

In conclusion, omics-based drug repurposing emerges as a promising alternative to *de novo* drug development, offering the potential to expedite the delivery of compounds to patients. Leveraging machine-learning and artificial intelligence methodologies to integrate the vast array of publicly available SLE omics data holds significant promise for advancing drug repurposing efforts in the treatment of SLE.

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