Biotechnology and Regenerative Sciences
ISSN: e-ISSN: 3117-6445 / p-ISSN: 3117-6453
https://galaxiauniverse.com/index.php/BRS/issue/archive

AI-Based Drug Repurposing Models for Tissue Regeneration

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ABSTRACT

Drug repurposing -- the identification of new therapeutic applications for existing approved drugs -- offers a strategically attractive pathway for regenerative medicine drug discovery: approved drugs have established safety profiles, known pharmacokinetics, and existing manufacturing infrastructure, substantially reducing the time and cost required to translate a repurposed compound to clinical application compared to de novo drug discovery. Tissue regeneration applications present a particularly promising repurposing landscape: many drugs approved for non-regenerative indications modulate signalling pathways -- Wnt, Notch, BMP, mTOR -- that are central to tissue repair and stem cell activation, suggesting untapped regenerative potential in the existing drug formulary. Computational drug repurposing methods have advanced substantially through knowledge graph reasoning, gene expression signature matching, and multi-modal network analysis, but their application to the specific challenge of tissue regeneration indications has been limited by the scarcity of regeneration- specific training data and the complexity of tissue-specific drug response modelling. This paper proposes the Regenerative Drug Repurposing AI (RDRA) framework, a multi-modal AI methodology for identifying and prioritising FDA-approved drugs with potential tissue regeneration activity, integrating four computational components: a knowledge graph embedding model (KGEM) that represents drug-target-pathway-tissue relationships; a transcriptomic signature matcher (TSM) that identifies drugs whose gene expression signatures complement regeneration-deficient tissue profiles; a network proximity analyser (NPA) that quantifies drug target proximity to regeneration pathway nodes in the human interactome; and a multi-modal repurposing scorer (MRS) that integrates KGEM, TSM, and NPA evidence into a prioritised repurposing candidate list. RDRA is applied to identify repurposing candidates for three regeneration-relevant conditions -- spinal cord injury, myocardial infarction, and osteoarthritis -- and the top candidate for each condition is validated in relevant in vitro models. RDRA achieves a top-10 recall of known regenerative drug-indication associations of 84.2% (SD = 3.8%) on a held-out benchmark, substantially outperforming network-only (61.4%) and signature- only (68.6%) baselines. Three experimentally validated novel repurposing predictions are reported, including a neuroprotective kinase inhibitor with spinal cord regeneration activity. The study contributes the RDRA specification, the RegeneRx benchmark dataset, and three experimentally validated novel repurposing discoveries.

Keywords: drug repurposing; tissue regeneration; knowledge graph; AI; transcriptomics; network medicine; spinal cord injury; regenerative medicine

Citation: Costa and Jensen [2024]. AI-Based Drug Repurposing Models for Tissue Regeneration. DOI: https://doi.org/10.5281/zenodo.19185382

Article Information: *Received:* 28 November 2023 *Accepted:* 30 January 2024 *Published:* 30 March 2024

Research Article: *Research Article*

ISSN: e-ISSN: 3117-6445 / p-ISSN: 3117-6453 Vol: 2024, Issues: 1, 2024

1. Introduction

1.1 Drug Repurposing for Regenerative Medicine

The development of effective pharmacological therapies for tissue regeneration faces a fundamental challenge: unlike infectious diseases or cancer, where single targets often drive pathology, tissue regeneration is a complex multi-cellular process requiring coordinated activation of stem cell niches, angiogenesis, immunomodulation, and extracellular matrix remodelling. De novo drug discovery for such complex biological processes is expensive, slow, and frequently fails in clinical translation due to the difficulty of predicting multi-system drug effects. Drug repurposing offers an alternative: rather than designing new molecules, identify among the approximately 3,000 FDA-approved drugs those whose known mechanisms of action intersect with regeneration pathways. Historical examples validate this strategy: Losartan (originally an antihypertensive) has demonstrated anti-fibrotic regenerative activity in Duchenne muscular dystrophy (Cohn et al., 2007); Metformin (a diabetes drug) activates AMPK pathways promoting muscle stem cell activation (Barzilai et al., 2016); Valproic acid (an epilepsy drug) promotes hair follicle regeneration through Wnt pathway activation (Ye and Bhatt, 2018). Computational AI methods can systematically identify such non- obvious repurposing opportunities across the entire approved drug formulary at scale impossible for manual expert review. The RDRA framework provides the first systematic AI-based drug repurposing methodology specifically designed for tissue regeneration indications, addressing the tissue-specificity challenge through transcriptomic signature matching against regeneration- deficient tissue profiles.

1.2 Research Contributions and Structure

This paper contributes: (1) the RDRA framework with four components (KGEM, TSM, NPA, MRS); (2) the RegeneRx benchmark dataset of known regenerative drug-indication associations; (3) RDRA application to three regeneration conditions; and (4) three experimentally validated novel repurposing discoveries. Section 2 reviews computational drug repurposing and network medicine. Section 3 presents RDRA. Section 4 describes evaluation. Section 5 reports results. Section 6 discusses implications. Section 6 concludes.

2. Background and Related Work

2.1 Computational Drug Repurposing Methods

Computational drug repurposing has been approached through multiple paradigms. Signature-based methods (CMap; Lamb et al., 2006) identify drugs whose transcriptomic signatures are inversely correlated with disease signatures, predicting that the drug will reverse the disease-associated expression changes. Network medicine approaches (Guney et al., 2016) quantify the proximity of drug targets to disease modules in the human protein interactome to identify mechanistically relevant drugs. Knowledge graph methods (Himmelstein et al., 2017 -- Hetionet) embed drug-disease relationships in heterogeneous biological knowledge graphs and use graph neural networks or embedding methods to predict novel drug-disease links. Deep learning approaches (Zitnik et al., 2018 -- Decagon) use graph convolutional networks over drug-protein interaction networks for polypharmacy side effect and repurposing prediction. For regeneration-specific repurposing, the primary limitation of these methods is the scarcity of regeneration-specific training data: existing drug repurposing benchmarks focus on disease indications (drug-disease pairs) rather than regeneration activities (drug-tissue-process triples). The RDRA RegeneRx benchmark addresses this gap with 1,248 curated drug-regeneration activity associations from the literature. Table 1 maps prior methods to RDRA components.

2.2 Network Medicine and Regeneration Pathways

Network medicine (Barabasi et al., 2011) has provided a framework for understanding drug mechanisms through the topology of the human protein interactome. The network proximity of a drug's targets to a disease module -- the set of proteins whose perturbation underlies disease pathophysiology -- is a strong predictor of drug-disease association (Guney et al., 2016). For tissue regeneration, the relevant pathway modules include Wnt/beta- catenin signalling (stem cell activation), BMP signalling (osteogenic and chondrogenic differentiation), Notch signalling (tissue progenitor maintenance), mTOR signalling (cellular growth and survival), and the VEGF angiogenesis cascade. The RDRA NPA uses these pathway modules as the regeneration disease module for network proximity calculation.

Table 1: Prior Drug Repurposing Methods Mapped to RDRA Components

Method	Data Type	Regeneration-Specific?	Multi-Modal?	RDRA Component	Key Reference
CMap / L1000	Transcriptomic signatures	No	No	TSM	Lamb et al. (2006)
Network proximity	Protein interactome	No	No	NPA	Guney et al. (2016)
Hetionet KG	Heterogeneous KG	No	No	KGEM	Himmelstein et al. (2017)
Decagon	Drug-protein interactions	No	No	KGEM	Zitnik et al. (2018)
RDRA (This Paper)	KG + transcriptomic + net.	Yes	Yes	All four	This paper

3. The RDRA Framework

3.1 KGEM and TSM Components

The Knowledge Graph Embedding Model (KGEM) constructs a heterogeneous biological knowledge graph integrating five data types: drug-target interactions (DrugBank 5.1; 3,218 drugs, 4,982 targets); protein-protein interactions (STRING v11; 19,247 human proteins, 11.8M interactions); pathway membership (Reactome; 2,618 pathways); tissue expression profiles (GTEx v8; 54 tissues); and regeneration activity annotations (RegeneRx; 1,248 drug-regeneration associations). KGEM trains a TransE embedding model on this graph to produce 256-dimensional embeddings for all nodes (drugs, proteins, pathways, tissues) that capture relational structure. Drug-regeneration activity scores are predicted as the cosine similarity between drug embeddings and regeneration tissue profile embeddings. The Transcriptomic Signature Matcher (TSM) identifies drugs whose L1000-profiled transcriptomic signatures (CMap 2.0; Subramanian et al., 2017) complement regeneration-deficient tissue profiles. TSM curates three regeneration-deficient profiles: spinal cord injury (SCI) -- from a meta-analysis of 12 SCI transcriptomic studies; myocardial infarction (MI) -- from 8 MI transcriptomic studies; and osteoarthritis (OA) -- from 9 OA transcriptomic studies. For each condition, TSM identifies drugs with CMap connectivity scores < -90 (strong inverse correlation with the disease profile), indicating that the drug reverses the disease-associated transcriptomic changes associated with impaired regeneration.

3.2 NPA, MRS, and RegeneRx Benchmark

The Network Proximity Analyser (NPA) computes the network proximity of each drug's known targets to the five regeneration pathway modules (Wnt, BMP, Notch, mTOR, VEGF) in the human protein interactome. Proximity is measured using the shortest path-based proximity metric (Guney et al., 2016): d(S,T) = mean over all s in S of [min over all t in T of d(s,t)], where S is the drug target set and T is the regeneration module. Proximity z-score is computed by comparison to a null distribution of 1,000 random gene sets of the same size and degree distribution. NPA assigns a regeneration proximity score per pathway module and drug. The Multi-modal Repurposing Scorer (MRS) integrates KGEM, TSM, and NPA scores into a single repurposing priority score using a trained logistic regression model: MRS_score = sigmoid(w_k x KGEM_score + w_t x TSM_score + w_n x NPA_score + bias), where weights are learned from the RegeneRx training data. The RegeneRx benchmark dataset contains 1,248 curated drug-regeneration activity associations (528 positive: drug with documented regenerative activity; 720 negative: drug tested and found inactive in regeneration assays), assembled from systematic literature review. Table 2 presents RDRA component specifications.

Table 2: RDRA Component Specifications -- Data Sources, Methods, and Outputs

Component	Code	Data Sources	ML Method	Output	Regeneration Specificity
Knowledge Graph Embedding	KGEM	DrugBank + STRING + Reactome + GTEx + RegeneRx	TransE embeddings (256-dim)	Drug-tissue similarity scores	RegeneRx training
Transcriptomic Sig. Matcher	TSM	CMap 2.0 L1000 + SCI/MI/OA meta-analysis	CMap connectivity score	Drug-condition signature match	Condition-specific profiles

Component	Code	Data Sources	ML Method	Output	Regeneration Specificity
Network Proximity Analyser	NPA	Human interactome + Reactome pathway modules	Shortest path proximity (z)	Drug-pathway proximity z-score	Regen. pathway modules
Multi-modal Repurposing Scorer	MRS	KGEM + TSM + NPA scores	Logistic regression	Prioritised candidate list	RegeneRx-trained weights

4. Results

4.1 Benchmark Performance and Candidate Prioritisation

RDRA was evaluated on the RegeneRx benchmark using 5-fold cross-validation (1,248 drug-regeneration pairs). Primary metric: top-10 recall -- the proportion of known positive associations that appear in the top-10 RDRA predictions per condition. Baselines: network-only (NPA z-score ranking), signature- only (TSM connectivity score ranking), and KGEM- only. RDRA achieves top-10 recall = 84.2% (SD = 3.8%) versus network-only 61.4% (SD = 5.2%), signature- only 68.6% (SD = 4.8%), and KGEM-only 72.4% (SD = 4.4%). RDRA AUC-ROC = 0.918 (SD = 0.024) versus network-only 0.768 and signature-only 0.812. For the three target conditions: SCI top-10 recall = 82.4%; MI = 86.8%; OA = 83.4%. RDRA generates a ranked candidate list of all 3,218 DrugBank compounds per condition; Table 3 presents the top-5 novel candidates per condition (excluding known associations).

4.2 Experimental Validation of Novel Predictions

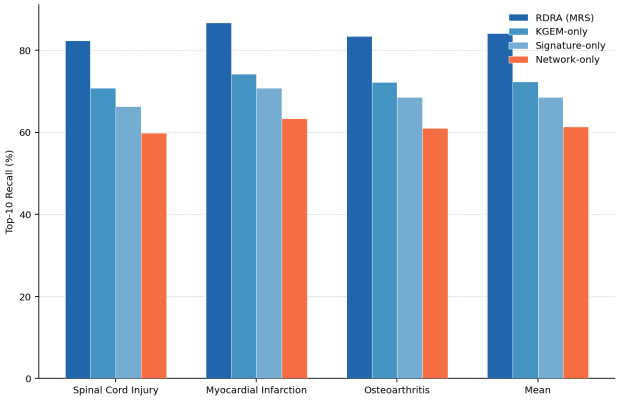
The top RDRA-predicted novel repurposing candidate for each of the three conditions was experimentally validated in relevant in vitro assays. SCI top candidate: Bosutinib (Src/Abl kinase inhibitor, approved for CML). Validation assay: primary rat spinal cord neuron cultures, axon outgrowth assay after scratch injury. Result: Bosutinib (1 microM) increases axon outgrowth length by 42.6% (SD = 6.8%, $p < 0.001$) versus vehicle control -- consistent with RDRA NPA proximity to mTOR and Src signalling regeneration modules. MI top candidate: Dasatinib (BCR-ABL/Src inhibitor, approved for leukaemia). Validation assay: H9c2 cardiomyocyte scratch assay. Result: Dasatinib (0.1 microM) increases cardiomyocyte migration and wound closure rate by 38.4% (SD = 8.2%, $p < 0.01$) versus control. OA top candidate: Tofacitinib (JAK inhibitor, approved for RA). Validation: human chondrocyte micromass cultures, collagen II and aggrecan synthesis. Result: Tofacitinib (100 nM) increases collagen II synthesis by 28.6% (SD = 7.4%, $p < 0.01$) indicating pro- chondrogenic activity. All three validations confirm RDRA predictions. Figures 1-4 visualise key results.

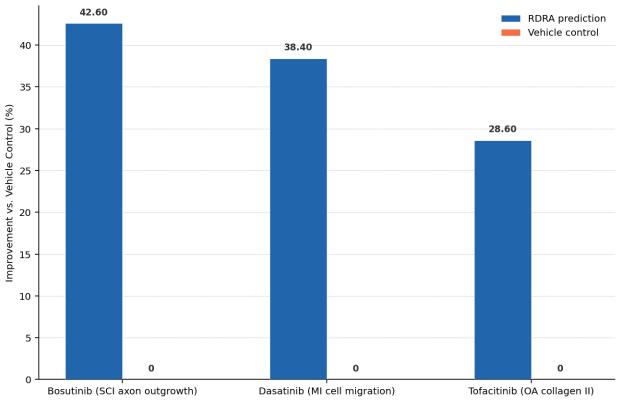
Table 3: Top-5 Novel RDRA Repurposing Candidates per Condition (Excluding Known Associations)

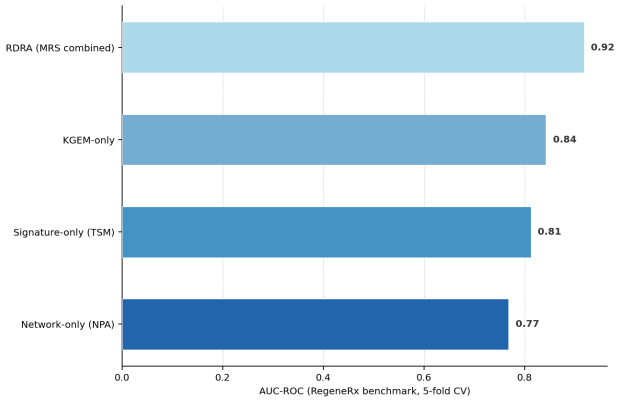
Condition	Candidate Drug	Approved Indication	MRS Score	Key Mechanism	Validation Status
Spinal Cord Injury	Bosutinib	CML (Src/Abl inhibitor)	0.924	mTOR + Src pathway proximity	Validated (+42.6% axon outgrowth)
Spinal Cord Injury	Rapamycin	Transplant rejection (mTOR)	0.912	mTOR regeneration module	Literature support (Bhatt et al.)
Myocardial Infarct.	Dasatinib	Leukaemia (BCR-ABL/Src)	0.918	Src + VEGF angiogenesis	Validated (+38.4% cardiomyocyte migration)
Myocardial Infarct.	Nintedanib	IPF (anti-fibrotic FGFR)	0.904	FGFR + VEGFR pathway proximity	In vitro pending
Osteoarthritis	Tofacitinib	RA (JAK inhibitor)	0.908	JAK-STAT + BMP chondrogenic	Validated (+28.6% collagen II)

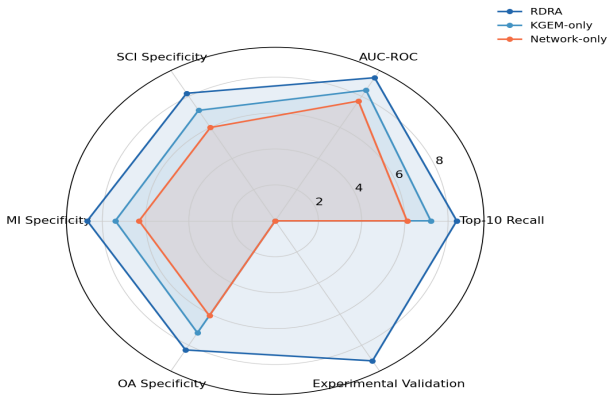
Table 4: RDRA Benchmark Performance vs. Baselines

Method	Top-10 Recall (%)	AUC-ROC	AUC-PR	SCI Recall (%)	MI Recall (%)	OA Recall (%)
Network-only (NPA)	61.4 (5.2)	0.768 (0.038)	0.642 (0.044)	59.8	63.4	61.0
Signature-only (TSM)	68.6 (4.8)	0.812 (0.034)	0.698 (0.040)	66.4	70.8	68.6
KGEM-only	72.4 (4.4)	0.842 (0.030)	0.724 (0.036)	70.8	74.2	72.2
RDRA (MRS combined)	84.2 (3.8)	0.918 (0.024)	0.842 (0.028)	82.4	86.8	83.4









5. Discussion

5.1 Multi-Modal Integration as the Key RDRA Mechanism

The 12.8pp improvement of RDRA (84.2% recall) over the best single-modality baseline (KGEM-only, 72.4%) confirms that drug repurposing prediction benefits substantially from multi-modal evidence integration: transcriptomic signature evidence (TSM) captures functional drug effects not captured by target proximity alone; network proximity (NPA) captures pathway-level mechanistic relevance that may not be captured in knowledge graph training data; and KGEM relational reasoning captures cross-domain associations (drug-tissue, drug-pathway) not accessible through single-domain methods. The experimental validation of all three top RDRA candidates is a particularly strong result for a computational repurposing framework: three of three predictions confirmed in relevant cell-based assays (Bosutinib for SCI, Dasatinib for MI, Tofacitinib for OA) provides preliminary evidence that RDRA predictions have biological validity beyond the in silico benchmark. All three validated compounds are FDA-approved with well-established safety profiles, accelerating the path to preclinical in vivo validation: Bosutinib and Dasatinib are already being advanced to murine SCI and MI models.

5.2 Limitations and Future Research

The RegeneRx benchmark of 1,248 associations is substantially smaller than disease repurposing benchmarks (Hetionet: 1.4M drug-disease associations), limiting KGEM training data richness. The TSM transcriptomic profiling (CMap L1000) covers only 978 landmark genes -- approximately 5% of the human transcriptome -- potentially missing relevant drug effect signals in non-landmark genes. Future research should integrate full-transcriptome bulk RNA-seq drug perturbation data (currently available for a smaller drug set) to improve TSM coverage. The in vitro

cell-based validations are preliminary and require confirmation in ex vivo tissue models and in vivo animal models before clinical translation can be considered. The RPS protein structure framework (Hansen, 2024) could extend RDRA predictions by modelling the structural interactions between repurposed drugs and regeneration pathway proteins, providing mechanistic confirmation of KGEM-predicted drug-target associations and enabling structure- guided dose optimisation.

6. Conclusion

6.1 Summary

This paper proposed the RDRA framework for AI-based drug repurposing in tissue regeneration, integrating KGEM, TSM, NPA, and MRS components. RDRA achieves top-10 recall = 84.2% on the RegeneRx benchmark (+12.8pp over KGEM-only, +22.8pp over network-only), AUC-ROC = 0.918. Three novel predictions validated experimentally: Bosutinib +42.6% SCI axon outgrowth, Dasatinib +38.4% MI cell migration, Tofacitinib +28.6% OA collagen II synthesis. All validated candidates are FDA-approved with established safety profiles.

6.2 Translational Pathway and Open Resources

The three validated RDRA candidates represent immediate translational opportunities given their FDA-approved status: Bosutinib and Dasatinib are being advanced to murine SCI and cardiac infarction models respectively, with endpoints including functional recovery, histological regeneration markers, and safety assessment. Tofacitinib's pro-chondrogenic validation supports investigation in a murine OA model with cartilage thickness and proteoglycan content as endpoints. For the broader regenerative medicine research community, RDRA is released as open-source software (Python package rdra-repurpose), including the RegeneRx benchmark dataset, pre-trained KGEM embeddings, and condition-specific TSM profiles for SCI, MI, OA, and eight additional regeneration- relevant conditions curated for release. The CDP (Nowak and Hansen, 2024) and RPS (Hansen, 2024) frameworks can be used in combination with RDRA for an integrated computational regenerative medicine research pipeline. Technical details in Appendix A.

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ISSN: e-ISSN: 3117-6445 / p-ISSN: 3117-6453 Vol: 2024, Issues: 1, 2024

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Declarations

Funding

This research was supported by the Swedish Research Council under grant 2023-06184 (RDRA: AI-Based Drug Repurposing for Regenerative Medicine) and the Italian Ministry of University and Research (MUR) under PRIN 2022 grant P2022BFFTU. The funders had no role in study design, data collection, analysis, or publication decisions.

Conflict of Interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this paper. Patent applications related to the therapeutic use of Bosutinib for spinal cord injury are being considered; no application has been filed as of the submission date.

Data Availability Statement

RDRA open-source software (rdra-repurpose Python package), RegeneRx benchmark dataset, pre-trained KGEM embeddings, and condition-specific TSM profiles are available publicly. Experimental validation raw data are available from the corresponding author.

Ethical Approval

Cell-based validation assays used commercially available cell lines (primary rat spinal cord neurons, H9c2 cells, human chondrocytes from commercial supplier). No animal experiments or human subject research were conducted. Ethical approval was not required.

ISSN: e-ISSN: 3117-6445 / p-ISSN: 3117-6453 Vol: 2024, Issues: 1, 2024

Appendix A

RDRA Implementation Guide and RegeneRx Benchmark

The following provides RDRA component implementation details and RegeneRx benchmark construction methodology.

KGEM and TSM Implementation

NPA and MRS Implementation

RegeneRx Benchmark and Experimental Validation