A Novel Computational Modeling Framework to Analyze Synovial-Tissue Based Drug Targets and Diagnostic Biomarkers in Rheumatoid Arthritis

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Q1: Scientific Question & Purpose

Question: What genes or proteins are directly correlated to joint destruction in Rheumatoid Arthritis (RA)? How can specific drug targets & diagnostic biomarkers better treat & diagnose RA?

Purpose: To ID synovial tissue-based drug targets & diagnostic biomarkers by creating & simulating an *in silico* mathematical model that provides a confirmed diagnosis of RA & assist in developing novel RA treatments

Hypothesis: Based on previous research, targeting VAV1, LCK, & CD4 is important as they are significantly upregulated in patients w/ RA & linked to tissue response/cartilage.

Q3: Data Analysis & Results

Perturbations that reduced JD:

| Pathway	Original Constant for Pathway	Perturbed Constant for Pathway	Change in Joint Degradation at time t = 4950
VAV1 activating CD4	K_22_24 = 1	K_22_24 = 0.01	9.984670e+11
MLT activating ROR	K_3_9 = 1	K_3_9 = 0.01	7.461039e+11
ROR activating Th-17	K_14_3 = 1	K_14_3 = 0.01	7.400516e+11
Th-17 activating IL-17	K_15_14 = 1	K_15_14 = 0.01	1.167708e+10
LCK activating CD4	K_22_21 = 1	K_22_21 = 0.01	7.606287e+11
Thymocytes activating CD4	K_22_23 = 1	K_22_23 = 0.01	1.055373e+12
VAV1 activating CD4	K_22_24 = 1	K_22_24 = 0.01	9.984670e+11
LCK activating Thymocytes	K_23_21 = 1	K_23_21 = 0.01	1.061217e+12

Perturbations that increased JD:

Pathway	Original Constant for Pathway	Perturbed Constant for Pathway	Change in Joint Degradation at time t = 4950
MLT activating ROR	K_3_9 = 1	K_3_9 = 100	1.148312e+12
TNF-α activating REV-ERB	K_4_2 = 1	K_4_2 = 0.01	1.109264e+12
ROR activating Th-17	K_14_3 = 1	K_14_3 = 100	3.453803e+13
REV-ERB inhibiting Th-17	K_14_4 = 1	K_14_4 = 0.01	1.481887e+12
CD4 activating Th-17	K_14_22 = 1	K_14_22 = 100	1.146315e+14
Th-17 activating IL-17	K_15_14 = 1	K_15_14 = 100	1.073755e+14
DEC2 activating IL1β	K_17_7 = 1	K_17_7 = 100	1.121071e+12
NF-kB activation IL-1/IL-6/MMP3	K_18_5 = 1	K_18_5 = 100	1.121270e+12
LCK activating CD4	K_22_21 = 1	K_22_21 = 100	1.147978e+12

Novel RA Model:
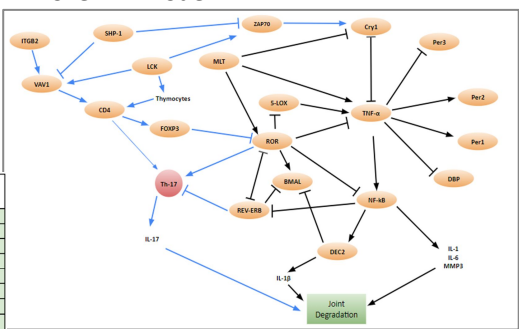
Concentrations at Various Time Increments:
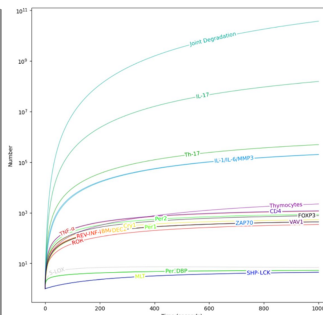
A novel framework, targeting pathways directly related to joint destruction was created with potential to find drug targets & diagnostic biomarkers

Q2: Methodology & Design

- **Software:** Google Colab, Python, Numpy/Pandas/seaborn library, matplotlib pyplot & label lines function
- Constructed ordinary differential equations (ODEs) for 30 gene networks & 25 molecules
- Constants: degradation, dilution, transcription, & interaction
- From research, 9 unique pathways of interest added
- Altered dynamics to ID drug targets & diagnostic biomarkers
- 92 perturbations on 46 constants incorporated
- 2 possible perturbations for interaction constants = 100, 0.01 **(IV)**
- Recorded perturbations w/ significant fluctuations in magnitude fold change or concentration differences over time **(DV)**

Q4: Conclusion & Interpretation

Potential Drug Targets–reduced JD: Inhibition of VAV1-CD4, LCK-Thymocyte, MLT-ROR, ROR-Th 17, Th-17-IL-17, & LCK-CD4

Diagnostic Biomarkers- increased JD: Activation of MLT-ROR, DEC2-IL1□, NF-kB-interleukin, & LCK-CD4; Inhibition of NF-α-REV-ERB & REV-ERB-Th-17

Strengths: Incorporated various interactors, accessible measurements, novel pathways studied, all possible perturbations tested

Limitations: constants derived from assumptions, "1" used as comparative value

Future Work: Running RNA sequencing, single-cell sequencing, binding assays, finding molecular weights, & incorporating AI-based techniques to ensure concentrations & constants are accurate; confirm results in vitro

Implications: Develop therapeutics & diagnostic tools for RA