Mechanism-based Inference of Drugs to Diseases using Drug-driven Ontologies and Semantic Infrastructure

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Strategies:

1. Identify drug targets that can be modulated by compounds

2. Identify new indications for existing drugs

“the most fruitful basis for the discovery of a new drug is to start with an old drug”

-James Black, Nobel laureate
Drug-Disease Correlation Ontology Model

Diagram showing the relationships between Drug, Drug-Disease Correlation Ontology, Drug-Disease Correlation, Disease, and various attributes such as Dose Regimen, Structure Classification, Therapeutic Category, Mechanism Of Action, Clinical Effect, Pharmacological Property, PK/PD/Toxicity, Pathway, Gene, Gene product, Cell, Phenotype, Disease Classification, Anatomy, Molecular Basis, Clinical Finding, Clinical Property, GO, MeSH, NCI, ATC, MeSH, CTCAE, SNOMED, UMLS.
Points to many authoritative sites increases the hub scores

High Authoritative Score

Pointed by good hubs its authoritative score increases

RDF Subgraph: SLE + Tamoxifen

768 Entities
1050 Associations
Example Short Path that leads to high-ranking relationship between SLE and Tamoxifen

**Beneficial effects of the anti-oestrogen tamoxifen on systemic lupus erythematosus of (NZBxNZW)F1 female mice are associated with specific reduction of IgG3 autoantibodies.**

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**BACKGROUND:** Sex hormones have been shown to influence the immune system and to modify the course of autoimmune disorders. **OBJECTIVE:** To examine the effects of the oestrogen antagonist tamoxifen on the course of systemic lupus erythematosus (SLE) in (NZBxNZW)F1 mice. **METHODS:** Groups of 8 week old (NZBxNZW)F1 female mice were treated with tamoxifen (800 micro g/mouse; twice a week) or with double distilled water for four months. Mice were evaluated monthly for the presence of autoantibodies directed against DNA and nuclear extract (NE) by enzyme linked immunosorbent assay (ELISA). White blood cells and thrombocytes were quantified by a cell counter and proteinuria by combistix kit. At 6 months of age, all mice that did not die spontaneously were killed and evaluated for the presence of glomerular immune deposits by indirect immunofluorescence assay. IgG isotypes of autoantibodies in the mouse sera and glomeruli were determined by gamma chain specific antibodies. **RESULTS:** Tamoxifen treatment significantly reduced autoantibody production directed against either NE or DNA. The latter reduction was mainly in autoantibodies of the IgG3 isotype. Furthermore, tamoxifen had significant beneficial effects on the course of SLE in (NZBxNZW)F1 mice. At 6 months of age, 40% of the untreated mice died spontaneously, whereas all the tamoxifen treated mice were still alive. All untreated mice showed severe thrombocytopenia and persistent proteinuria, with diffuse glomerular immune deposits of IgG2a and IgG3 isotypes in their kidneys. In contrast, the tamoxifen treated mice had a normal number of thrombocytes and only minimal proteinuria. Moreover, glomerular immune deposits were detected in <40% of the tamoxifen treated mice. The latter were mainly of the IgG2a but not of the IgG3 isotype. **CONCLUSION:** The results clearly show the remarkable therapeutic effects of tamoxifen on SLE of (NZBxNZW)F1 female mice and suggest that these beneficial effects are related to the specific reduction of IgG3 autoantibodies.
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