A Focused Noble Metal Based Chemical Library for the Discovery of Drugs that Inhibit Autoimmune Responses

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Technology description

Summary

Background
Autoimmune diseases result when the immune system becomes over-active and attacks the body itself. Autoimmune diseases as a family (over 80 separate diseases) affect 14.7 to 23.5 million people in this country, and for reasons unknown, their prevalence is rising. The most prominent autoimmune diseases include rheumatoid arthritis, lupus, psoriasis, multiple sclerosis, and type I diabetes. Gold and platinum have been used to treat autoimmune diseases such as lupus and rheumatoid arthritis since the 1930s, although the mechanism of action was unknown. Traditionally, gold therapy has been cheap and effective (it can cause complete remission in 20% of cases). However, associated adverse side effects diminished its use and a lack of previous knowledge of how the therapy works limited further development. Invention Rheumatoid arthritis (RA) is a debilitating example of an autoimmune disease caused by misguided MHC (major histocompatibility complex) class II molecules triggering the attack of joint collagen. CU researcher Brian DeDecker, in previous work, used a quantitative assay measuring the release of antigenic peptide from MHC class II proteins to screen a large library of compounds. He found that noble metals, such as Au(III), efficiently release antigenic peptide from class II MHC′s in an allosteric reaction. This discovery, along with other data, provided an important and testable molecular mechanism to explain how commonly used "gold therapy" inhibits the autoimmune response associated with RA. The demonstration that noble metals in a specific oxidation state efficiently strip peptide antigens from class II MHC′s provides a template for improving traditional "gold therapy" and for reducing its associated side-effects. One strategy is to develop a metal based compound that has a higher affinity and more specificity for the alleles of class II MHC′s that are directly associated with RA. To identify such a compound, there is a need for a focused chemical library built on a backbone of these noble metals with a wide range of ligands attached — initial studies show that added ligands do not inhibit the release of antigenic peptides, and may provide more specificity and lower toxicity. Such a library would be crucial for the identification of a next generation gold therapy drug for the treatment of RA. Members of this library would be assayed for their ability to strip peptides from the MHC class II molecules associated with RA (DR1 and DR4). The CU team has a well-defined high-throughput screen for this. The quantitative results of the assay allow for the selection of

compounds with higher activity from the library. The increased activity of the identified compound could be caused by new contacts formed between the functional group added to the metal and the surface of the MHC class II protein. To identify complexes that are allele specific, these high affinity lead compounds would be assayed against other MHC class II alleles not associated with RA. Such an allele-specific molecule may have fewer side effects and could prove to be more useful as a therapeutic.

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