CALIFORNIA STATE SCIENCE FAIR
2012 PROJECT SUMMARY

Name(s)

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Project Number

S0514

Project Title

In vivo Drug Assembly

Abstract

Objectives/Goals

Fragment-based drug design is used to construct single high affinity drugs from many small, low affinity components. A pervasive problem with such drugs is binding to receptors at disease sites and in other healthy parts of the body with deleterious side effects. We design drugs comprised of similar small components that bind to receptors at the disease site and proteins present only at the target. The approach is illustrated for Rheumatoid Arthritis (RA). Conventional drugs like Enbrel inhibit TNF receptors in the diseased joints and in healthy parts of the body. Type II collagen is present only in joints, save for trace amounts in the eyes and ears. Our redesign of Enbrel binds to both TNF receptors and to Type II collagen, resulting in unprecedented precision in targeting desired drug action to joints.

Methods/Materials

We performed a number of binding affinity calculations. For a two fragment drug like Enbrel, we calculated the percentage of each fragment that will bind to a receptor and the percentage of the assembled drug that will bind to the disease-area-localized assembly protein and to the receptor at chemical equilibrium. We used this information to compute the percentage of bound receptors given specified affinities and drug and organizer molecule concentrations, permitting the calculation of the ratio of bound receptors in the target area to bound receptors outside it. We used the public domain program Autodoc to build molecular models for Enbrel, Type II collagen alpha helices, and TNF receptors and set flexible residues for Type II collagen at the ends where it tends to be more flexible. We then used the public domain program Vina to calculate the affinity of Enbrel alone to a TNF receptor and of the alpha helix/Enbrel molecule to both local Type II collagen and a nearby TNF receptor. We took the resulting affinities and plugged them into our earlier calculations to calculate the ratio of bound receptors inside to bound receptors outside the target region.

Results

We achieved ratios in above 10:1 with many in excess of 100:1, far above the ratios on the order of 1:1 attained by current drugs.

Conclusions/Discussion

Our results demonstrate the feasibility of designing drugs that confine their actions only to diseased areas in the body. We will use drug simulation programs next to predict and evaluate drug interactions within the body in concert with information from drug fragment libraries.

Summary Statement

We design drugs that target only diseased parts of the body by forcing them to bind to proteins present only at the target.

Help Received

Our parents helped by proofreading the paper and with the printing of our poster.