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Whilst Identifying Preferred Hot Spots for Ligand Binding

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Description

The deadly coronavirus disease 2019 (Covid-19) is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and poses a serious threat to public health. Through a contact between its spike protein (S-protein) and the human angiotensin-converting enzyme 2 receptor of its host, this virus infects cells and initiates viral fusion. The scientific community immediately paid attention to the inhibition of the interaction between the S-protein and hACE2 and the S-protein was considered the primary target for the creation of vaccines and affinity ligands for diagnostics and therapy. Numerous S-protein binders, ranging from antibodies derived from immunized patients to de novo designed ligands, have been rapidly reported, with some binders already showing promising in vivo protection against SARS-CoV-2.The following is a summary of affinity ligands designed, engineered, and natural that target the S-protein. The focus is on molecular recognition and the preferred hot spots for ligand binding. The findings of this review can be used to develop new affinity ligands for SARS-CoV-2 proteins or to enhance ligands that are already in use. In order to accelerate the discovery, production, and delivery of diagnostic, prophylactic, and therapeutic solutions in the event of subsequent pandemics, lessons learned from the Covid-19 pandemic must also be incorporated into the consolidation of protein engineering processes and tools.

Development of 9-mer Peptides to Bind with Fab Fragments

Due to the fact that they combine superior bio distribution and blood clearance with excellent targeting, antibody fragments and their engineered variants demonstrate true potential as next-generation therapeutics. However, in contrast to full antibodies, antibody fragments do not yet have a standard platform purification procedure that can be used for mass production. In affinity chromatography, short peptide ligands are viable alternatives to protein ligands. An integrated computational and experimental strategy for developing 9-mer peptides that bind to Fab fragments from scratch is described in this work. Human polyclonal Fab was used to test the first batch of designed sequences experimentally, and the best one was chosen as a prototype for in silico ligand refinement. Using human Fab- and Fab equilibrium and dynamic binding studies were carried out on chromatographic resins to evaluate the resulting peptides after they were conjugated. High product capture and recovery are facilitated by binding capacities of up to 32 mg of Fab per mL of resin with mild affinity found in equilibrium studies. Product yield values as high as 90% were found in dynamic studies. Purities ranged from 83 to 93% in the initial purification studies, and yields ranged from 11 to 89%. These findings provide a foundation for the development of these ligands in the direction of bio manufacturing translation in the future. Creating transcription-dependent biosensors necessitates locating, isolating, and obtaining naturally occurring transcription factors. However, it takes a lot of time and effort to find and optimize TFs for particular molecules. Consequently, we present a method for the de novo design of DLA, a non-natural TF, based on a subtle conformational change in the Ligand Binding Domain (LBD) following target molecule and receptor binding. In order to comprehend the complete activity of DLA, which involves shortening the distance between the DNA-Binding Domain (DBD) and the activation domain after progesterone binds to its LBD within DLA, we used molecular dynamics to simulate various conformational states of DLA for the de novo design of DLA. The simulated results suggested that prokaryotic B42 and prokaryotic LexA, a truncated LBD from the progesterone receptor, constitute TF-functioning DLA. An S. cerevisiae biosensor for the detection of progesterone was constructed using DLA as a transcription activator to control the transcription of green fluorescent protein as a proof of concept. The progesterone-explicit biosensor was effectively developed with a responsiveness record EC50 of 27 µg/L, working reach (0.16-60 µg/L) and time-to-discovery (2.5 h).In the end, a low-cost, easy-to-use kit for quickly detecting progesterone in the clinic was developed. Using the same approach, this work could theoretically be applied to the creation of additional biosensors.

Computationally Docking and Assembling Single Nucleotides

Because okadaic acid is a poison that causes diarrhea and is found in a lot of shellfish, finding it is very important for the safety of seafood. Biosensors employing nucleic-acid tamers as recognition molecules are emerging as an important detection tool due to their high sensitivity and low cost. However,

acquiring OA high-affinity aptamers through the conventional SELEX screening procedure takes a lot of time and resources. Alternately, we developed a new design strategy based on the target molecule's three-dimensional structure in this work. This method creates OA aptamers by computationally docking and then assembling single nucleotides (A, C, G, and T) without using experimental screening utilizing saturated molecular docking to identify the target molecule's high-affinity nucleotide binding sites forming binding units for the target molecule out of the bound nucleotides making full-length aptamers by inserting stabilizing units that link these binding units together. Five OA aptamers were constructed in this manner, and micro scale thermophoresis experiments confirmed that their Kd values range from 100 to 600 nM; Moreover, one of them, designated 9CGAT_4_a, may be able to bind specifically to OA while exhibiting low affinity for the other three marine bio toxins. As a result, this study provides aptamers with high affinity and specificity for the creation of OA biosensors and a promising de novo design strategy that can be applied to other target molecules. Even though many conventional de novo drug design strategies based on computational growth algorithms and evolutionary algorithms have been developed to generate novel molecular structures from building blocks many of these strategies fall somewhere in the middle of achieving multiple goals and producing novel compounds. The development of deep learning presents innovative drug design and discovery with new opportunities. Numerous DL-based de novo drug design algorithms have been developed in recent years. The successful use of DL in drug discovery was named one of the top 10 breakthrough technologies in 2020 by the Massachusetts Institute of Technology (MIT) Technology Review. The actual application of QSARdiscriminative modeling is the use of DL-based methods implemented in VS to predict the physiochemical or biological properties of the input molecules. When compared to the discriminative function that DL plays in VS, DL-based generative models can essentially be thought of as an explorer for finding compounds in the vast chemical space that possess desirable properties. The process of summarizing and extracting the properties and structural features of existing molecules in chemical space and then transforming them into novel scaffolds, also referred to as the reverse QSAR process, can be achieved by DL-based generative models. As shown in the right upper corner of the purpose of a generative model is somewhat similar to that of a VS method in that it employs optimized strategies to reach the desired molecular properties. On the other hand, a VS method typically employs a variety of filters to narrow the chemical space of the screened compounds until it reaches a tractable range. Nonetheless, it is thought that generative models can generate molecules with novel scaffolds and desirable properties by exploring the continuous space of properties.