NRC·CNRC

ADAPT platform for antibody affinity maturation (T-90201)

Highlights

The design of superior biologic therapeutics, including monoclonal antibodies, single domain antibodies, antibody fragments, engineered proteins and protein domains, involves optimizing their ability to bind to disease targets (antigens). Brute-force affinity optimization of biologics in a laboratory setting by selection or screening requires significant investment and provides limited control over the achievable affinity and stability; it also generates an incomplete understanding of a biologic's molecular interactions.

To aid in the selection and rationalization of mutants that improve and/or modulate the affinity of antibodies and other biologics, the NRC has developed an efficient platform called ADAPT (Assisted Design of Antibody and Protein Therapeutics). ADAPT interleaves computational predictions with experimental validation, significantly aiding the design of protein therapeutics by guiding the selection of optimal mutations.

Technology transfer

› R&D agreement for service or collaboration

Market applications

› Affinity maturation/modulation of protein therapeutics, which are used to treat a wide range of diseases

How it works

The first stage of the ADAPT platform exhaustively scans the protein

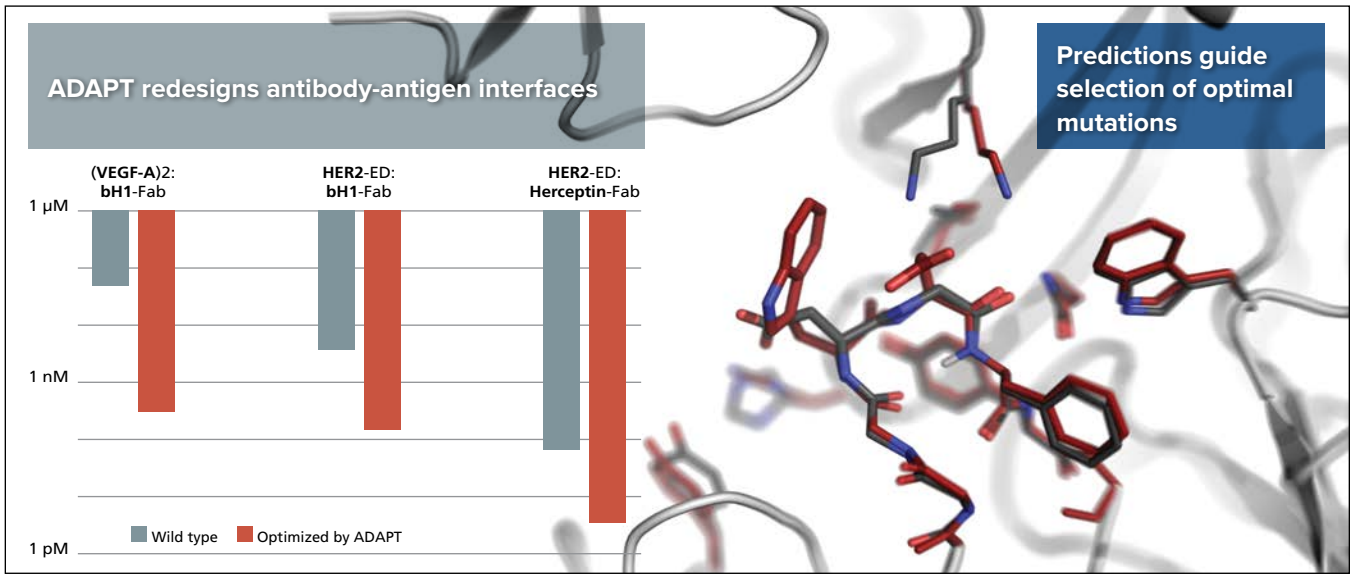

Figure 1: Examples of antibody fragments with various potencies of antigen binding that were affinity-matured by ADAPT (up to triple mutations required).

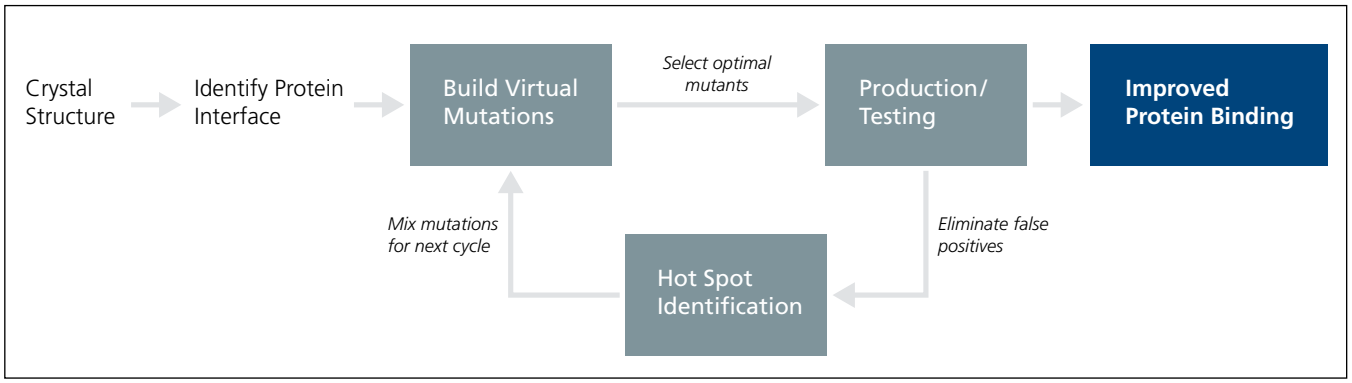

Figure 2: ADAPT mutagenesis workflow features an automated mutation screening stage. Predictions guide selection of optimal mutants through use of a web-based interface. Mutants are then produced to eliminate virtual false positives and identify hot spots. Mixing identified hot spots through subsequent rounds of ADAPT yields the optimal sequence.

interface, i.e. the complementarity determining region (CDR) of antibodies, creating virtual mutants using four computational methods: FoldX, Rosetta, SCWRL and SIE. A consensus model of a mutation is built in order to predict binding affinity and guide the selection of mutants for affinity maturation/modulation. A small number of single-point mutants are then produced and tested to eliminate false positives, leading to the identification of hot spots for affinity improvements. To reach the desired affinity change, a second iteration of ADAPT is run, creating new virtual mutations while weeding out non-additive pairings resulting from structural incompatibilities of the initial hot spots. The process continues with additional ADAPT cycles until affinity improvements level off. A typical ADAPT optimization process requires about 30 to 50 mutants, ranging from single to quadruple point mutations.

A client seeking to improve a protein's affinity will receive reports from the NRC at regular intervals, stating how many mutants have been generated and by how much their affinity has been improved. It typically takes at least double mutations in order for NRC experts to recommend the best ADAPT mutants that the client should take forward, with triple and quadruple mutants providing an advanced spectrum of candidates to choose from. The NRC will tailor the frequency of reporting based on the obtained results in order to best meet our clients' needs.

To access the technology, the crystal structure of the two interacting proteins (e.g., antibody-antigen complex) for which the client is seeking to increase affinity must be provided or be publicly accessible.

Benefits

- Save time and money by reducing the amount of brute-force affinity optimization in the lab
- Flexible design provides several well-characterized candidates
- Broad applicability to optimization of protein-protein interfaces in general
- Suitable for specificity optimization

Patents

NRC file 90201: Knowhow offered as R&D service or collaboration.

CONTACT
Daniel Desmarteaux
Client Relationship Leader
Tel.: 514-496-5300
Daniel.Desmarteaux@nrc-cnrc.gc.ca
www.nrc-cnrc.gc.ca/eng/rd/hht

NR16-171/2017E-PDF
ISBN 978-0-660-23913-2 PDF
ISBN 978-0-660-23914-9 PAPER
December 2017
Également disponible en français