Argonne NATIONAL LABORATORY | Technology Development & Commercialization

A Systematic Method to Improve Antibody Stability

Antibodies are proteins produced by humans and animals to defend against infection; antibodies can also be used to diagnose and treat some diseases and to detect toxins and pathogens. Global demand for antibody therapeutics — $25 billion in 2007 and as high as $45 billion by 2012 — makes it one of the fastest-growing sectors in the pharmaceutical industry.

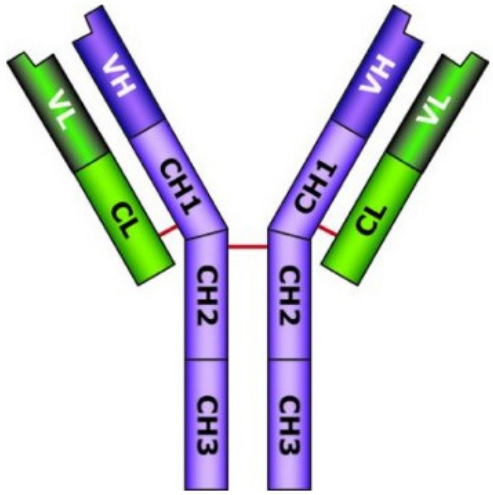
However, significant challenges still exist in application development: antibodies are fragile and short-lived outside of cooler, temperature-controlled environments. The majority of commercially available antibodies are relatively unstable. Their serum half-life is lower than that of naturally occurring antibodies, and their usefulness is usually limited to the laboratory because they require refrigeration for long-term preservation. Current methods of increasing the stability of antibodies are costly, time consuming and highly unpredictable.

Technology Description

Argonne researchers, led by senior biophysicist Fred Stevens (now retired), have developed a proprietary antibody engineering strategy to improve antibody stability. Work by an earlier research team led by Stevens had unexpectedly discovered that unstable, amyloid-forming antibody fragments (which occur in certain disease states) contain stabilizing as well as destabilizing amino acid variations. This finding launched the team into research on antibody stabilization.

When seven stabilizing amino acid changes were introduced into an amyloid-forming variable domain, a billion-fold improvement in thermodynamic stability was obtained, reflecting a much higher ratio of native protein folds to unfolded proteins — a major factor in antibody shelf life. The billion-fold improvement in thermodynamic stability increased the protein's thermal resistance to heating, with a "melting temperature" of about 70°C.

In focusing on a different antibody variable domain, 11 candidate amino acid changes were identified: four of these changes improved stability and, when combined together in the original domain, a 2,000-fold improvement in stability resulted. Results were comparable in a follow-up experiment using a functional antibody fragment. Both experiments were performed in a month's time, whereas most protein stabilization projects often require open-ended timeframes.



Potential Benefits

This new method is systematic, fast, inexpensive, and highly predictable. Stabilized antibodies with full functionality (e.g., as the basis for biosensors) could be used in diagnostic and detection kits that must operate in less-than-optimal environments, such as in airports and subway stations — places where the ongoing detection of pathogens is not possible at present because antibodies cannot tolerate the environmental conditions. The method can also be used to generate multiple products from the same antibody by fine-tuning stability levels. For instance, antibodies with low stability are well suited for imaging and radiotherapy applications. Antibodies with medium stability are preferred for therapeutic applications, and antibodies with high stability are desirable for diagnostic and biosensor applications.

Technology Area: Research tools
Product: A platform method for increasing antibody stability
Development Stage: Ready to transfer to industry for commercial application
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