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Understanding and overcoming trade-offs between antibody affinity, specificity, stability and solubility

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Highlights

- Antibodies display trade-offs between key properties during affinity maturation
- Antibody mutations that increase affinity are commonly destabilizing
- Affinity-enhancing mutations can reduce antibody specificity and solubility
- New methods are reported for minimizing trade-offs between key antibody properties

The widespread use of monoclonal antibodies for therapeutic applications has led to intense interest in optimizing several of their natural properties (affinity, specificity, stability, solubility and effector functions) as well as introducing non-natural activities (bispecificity and cytotoxicity mediated by conjugated drugs). A common challenge during antibody optimization is that improvements in one property (e.g., affinity) can lead to deficits in other properties (e.g., stability). Here we review recent advances in understanding trade-offs between different antibody properties, including affinity, specificity, stability and solubility. We also review new approaches for co-optimizing multiple antibody properties and discuss how these methods can be used to rapidly and systematically generate antibodies for a wide range of applications.

1. Introduction

Monoclonal antibodies (mAbs) are being used in diverse therapeutic and diagnostic applications due to several of their attractive properties (Fig. 1) [1-3]. The most important antibody properties relate to their natural functions, such as their high binding affinity and specificity mediated by their complementarity-determining regions (CDRs) within the variable regions (variable heavy, V_H, and variable light, V_L). Other key natural antibody properties include their effector functions – such as antibody-dependent cell-mediated cytotoxicity