LAMPIRE BIOLOGICAL LABORATORIES

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Custom Anti-Oligo-RNA Polyclonal Antibodies from LAMPIRE Biological Laboratories

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Introduction

The Ascendance of RNA-Based Therapeutics

The landscape of modern medicine has been fundamentally reshaped by the rapid ascent of oligonucleotide therapeutics. From the clinical success of antisense oligonucleotides (ASOs) to the burgeoning field of antibody-oligonucleotide conjugates (AOCs), RNAi-based modalities are providing solutions for previously "undruggable" targets (Damase et al., 2021). As these pipelines mature, the demand for robust bioanalytical tools has reached a critical inflection point. Specifically, highly sensitive anti-oligonucleotide antibodies have become indispensable for characterizing pharmacokinetics (PK), tissue-level biodistribution, and the assessment of anti-drug antibodies (ADAs) in regulated bioanalysis.

The First Challenge: Low Immunogenicity

Despite their utility, producing high-affinity antibodies against oligo-RNAi remains a significant challenge. Small RNAi fragments are inherently poor immunogens due to their low molecular weight and highly repetitive, negatively charged phosphodiester backbones. While rodent models often yield a restricted repertoire when challenged with these haptens, the rabbit immune system offers a distinct advantage.

Rabbits utilize unique mechanisms of gene conversion and somatic hypermutation, allowing for the development of antibodies with superior affinity and a broader diversity of paratopes than traditional murine hosts (Rodriguez et. al., 2025; Weber et. al. 2017). Consequently, leveraging the rabbit's innate immunological plasticity is not merely an alternative, but a strategic necessity for generating reagents required for modern RNAi-based bioanalysis.

The Second Challenge: Purification of Specific Anti-RNAi Antibodies

Purifying anti-oligo-RNAi antibodies introduces complexities that surpass the standard affinity workflows for antibodies against protein-based antigens. The high negative charge density of the RNAi antigen promotes non-specific binding with various serum proteins, leading to high background noise in sensitive assays like ELISA or IHC. Moreover, the presence of endogenous RNases in rabbit serum poses a constant threat to antigen integrity during affinity purification. Recent industry consensus emphasizes that standard Protein A/G capture is insufficient for these specialized reagents; achieving the necessary signal-to-noise ratio requires specialized, denaturant-free affinity chromatography to ensure the final reagent

maintains its integrity and functionality (Wojcik et.al 2025).

Production of Custom anti-RNAi Polyclonal Antibodies

LAMPIRE's Edge: High Titers in Rabbits immunized with Oligo-RNAis

Our proprietary immunization platform is engineered to overcome the low immunogenicity barrier of modified oligonucleotides. While industry data often shows anti-oligo titers plateauing at and below 2.0E+04, our protocols drive the humoral response to 1.0E+05.

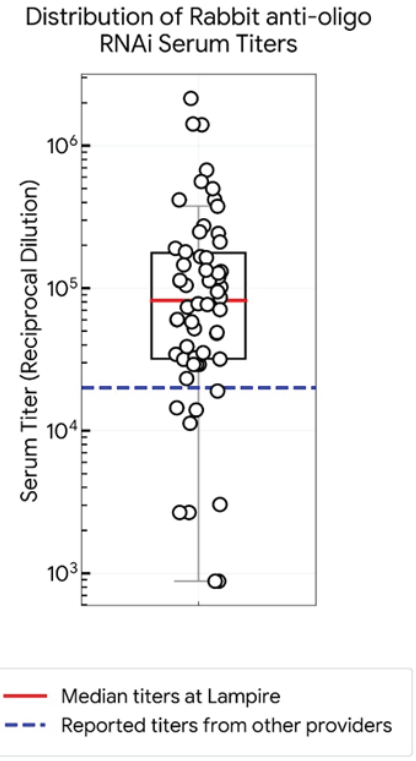

Figure 1: Distribution of serum titers against various oligo-RNAi antigens across 58 host animals. While we target high-titer responses, our platform maintains a minimum floor at 0.5E+04.

Affinity Antibody Purification: Capitalizing on High Titer Sera, and Rescuing Antibodies from Low Titer Sera

The achievable purity of polyclonal antibody preparations is intrinsically linked to the initial titer of the starting material. When dealing with low-titer sera, several biochemical and biophysical factors complicate the isolation of high-quality antibodies:

Competitive Binding and Ligand Availability

Affinity resins possess a finite density of binding sites. In high-titer scenarios, high-affinity antibodies rapidly saturate these ligands, effectively "crowding out" weaker, non-specific interactions. Conversely, in low-titer sera, a significant portion of the ligands remains unoccupied, providing an opportunity for lower-affinity serum proteins—such as albumin—to occupy these spaces and co-elute with the target.

Mass Action and Equilibrium Shift

Following the Law of Mass Action, the rate of a chemical reaction is proportional to the concentration of the reactants. A diminished concentration of the target antibody shifts the equilibrium, making the binding kinetics of the target less favorable when compared to the overwhelming mass of background impurities. This reduces the capture efficiency of the resin for specific anti-RNAi antibodies.

Impaired Mass Transfer and Surface Adsorption

In low-titer preparations, the ratio of spurious proteins to target antibodies is drastically skewed. Even with a resin selectivity of 99%, the sheer volume of non-specific proteins can impair the mass transfer of the target antibody into the affinity resin pores. Furthermore, this high concentration of background proteins increases the risk of surface adsorption onto the resin backbone (the matrix) itself, rather than the intended ligand.

To ensure the highest possible yield and cost-efficiency for our clients, our purification

platform utilizes a proprietary affinity chromatography workflow. By optimizing the capture phase on an antigen-immobilized resin followed by a highly efficient wash protocol, we effectively eliminate non-specific serum proteins while conserving expensive modified-RNAi antigens. Our gentle pH-shift elution (pH=3.0) allows for recovery of both high-affinity clones and low-abundance antibodies.

A useful method to monitor the specific antibody capture during the affinity purification is through titration ELISA. In Figure 2, the titration curves of a pre-purified sera with a titer of 9.41E+04 and the flow through fraction are compared. A comparison of the ELISA titration curves reveals that the post-capture flow-through exhibits a titer value **209 times lower** than that of the pre-purification serum. Assuming the functional avidity of the polyclonal pool remains constant between the two samples, this 200-plus-fold shift in functional titer indicates that the remaining "active" antibody concentration in the waste stream is approximately **1/209 (or 0.48%)** of the original starting material. Consequently, it can be inferred that over **99.5%** of the antigen-specific fraction was successfully partitioned onto the affinity matrix.

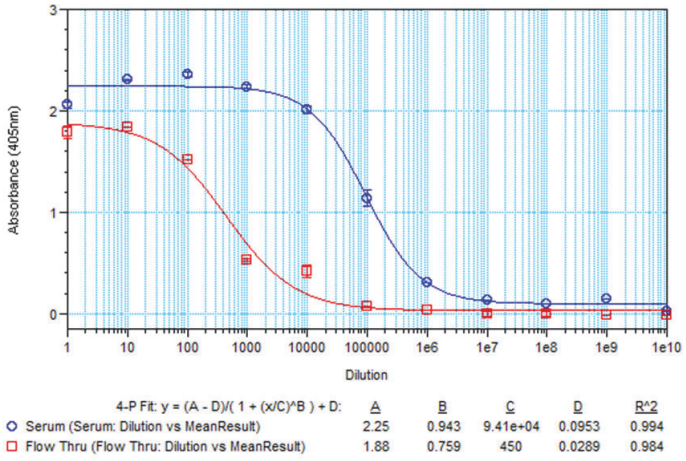

Figure 2: Representative dose-response curves for pre-purification serum (blue) and post-capture flow-through (red) against immobilized oligo-RNAis.

Data points were fitted using a four-parameter logistic (4PL) regression model. A 209-fold shift in the titer is observed in the flow-through, representing a depletion of >99.5% of the antigen-specific IgG from the bulk serum. These results assume constant functional avidity across both samples, correlating the loss of signal directly to a reduction in the absolute mass of the target antibody in the flowthrough.

Our purification platform consistently delivers antibodies of a purity of 95% and above (as judged by SDS-PAGE, Figure 3).

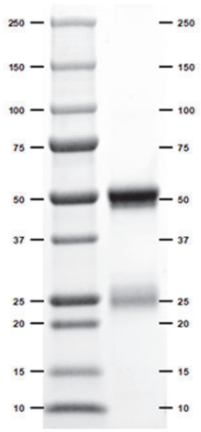

Figure 3: Reduced SDS PAGE analysis of an anti-oligo RNAi polyclonal antibody purified through affinity with LAMPIRE's method. The SDS PAGE gels are analyzed by densitometry, and the purity of the sample was determined to be 98%.

As demonstrated in the yield analysis below (Figure 4), LAMPIRE's method delivers specific yields up to 0.35 mg/mL of sera and remains robust enough to recover purified antibodies from low titer sera.

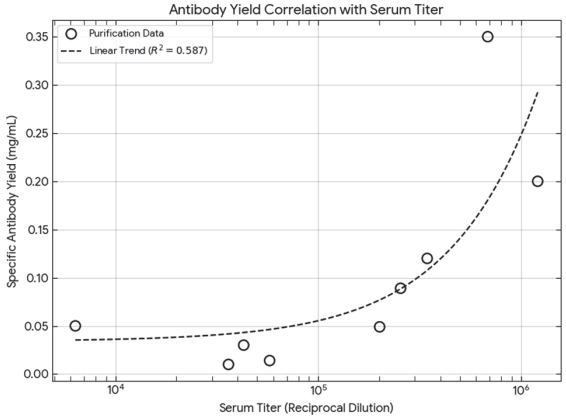

Figure 4: Specific Yield vs Serum Titers for different Custom anti-Oligo-RNAi projects. This figure demonstrates the scalability of our affinity purification process. The linear trend is shown for reference only.

Antibodies That Work: Immuno Analysis via ELISA

The ultimate metric of success for a custom anti-oligo-RNAi antibody is its performance in high-sensitivity immunological assays. The functional potency of our purified polyclonal antibodies is tested through ELISA.

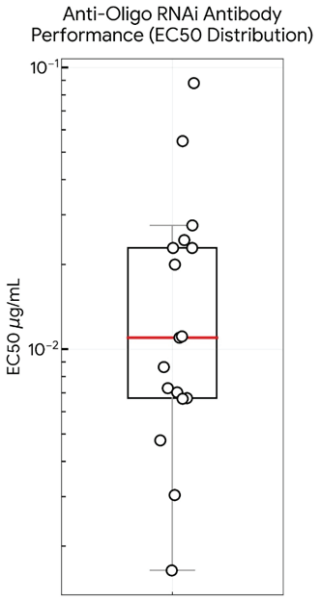

Figure 5: EC50 distribution of polyclonal anti-oligo-RNAi antibodies purified at LAMPIRE. Our purified anti-oligo-RNAi antibodies show EC50 values as low as 0.0016 µg/mL with a median of 0.011 µg/mL. These exceptionally low EC50 values serve as a quantitative benchmark for superior antibody avidity and sensitivity, ensuring our reagents can detect low oligo-RNAi therapeutic concentrations.

Empowering Next-Generation RNAi Bioanalysis through High-Avidity Rabbit Polyclonals

By combining custom rabbit immunization schedules with a cost-effective affinity purification platform, we provide a robust solution for the development of anti-oligo-RNAi antibodies. Our data demonstrates that we not only exceed industry benchmarks for serum titers but also offer a unique "rescue" capability for low-responder animals, delivering high-avidity antibodies essential for the next generation of RNAi therapeutics.

Literature Cited

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