Using somatic hypermutation for therapeutic monoclonal antibody development

By mimicking the critical features of somatic hypermutation *in vitro*, AnaptysBio has harnessed the natural diversity of the immune system to rapidly generate potent antibodies to emerging therapeutic targets.

AnaptysBio has utilized a new approach to discover and optimize monoclonal antibodies (mAbs) against therapeutic targets. The company has now announced seven antibody-development deals, and it is actively expanding an internal pipeline of antibodies in select therapeutic areas.

A key aspect of the adaptive immune system is the generation of antibodies by B cells after they are exposed to a new foreign element. Crucial to this process is the B cell receptor locus's ability to undergo somatic mutation at an extremely high rate—at least 10^5- to 10^6-fold higher than background—when B cells start to proliferate in response to an antigen. The biochemistry behind this process, which is called somatic hypermutation (SHM), was poorly understood until Michael Neuberger of the MRC Laboratory of Molecular Biology and Matthew Scharff of the Albert Einstein College of Medicine determined that activation-induced cytidine deaminase was responsible through its ability to act directly on DNA in the B cell.

Activation-induced cytidine deaminase mediates somatic hypermutation by nonrandomly deaminating cytosine into uracil at specific DNA motifs found within the antibody variable region. Conversion to uracil triggers error-prone DNA repair that frequently introduces point mutations, leading to antibody diversity.

Based on this discovery[1,2], AnaptysBio was formed in 2005 to replicate SHM *in vitro* as a platform technology for generating therapeutic mAbs (**Fig. 1**). The company coupled *in vitro* SHM with a pioneering mammalian cell display technology and has since applied it to more than 30 therapeutic antibody projects and published six peer-reviewed scientific papers related to this methodology[3–8]. Called SHM-XEL, the platform generates antibodies with much stronger functional potency than those generated in the body because AnaptysBio can apply selective pressure *in vitro* beyond that encountered *in vivo*.

SHM-XEL is able to generate mAbs against epitopes that were previously thought intractable and with potencies that are difficult to achieve with other technologies. For example, creating neutralizing mAbs through immunization of wild-type and transgenic animals can be difficult when antigens are well conserved or toxic to the animals. Microbial display technologies usually do not generate high-affinity mAbs without additional affinity-maturation steps, and antibody fragments isolated from microbial libraries can be difficult to reformat into well-expressed IgGs that are soluble enough for subcutaneous formulations.

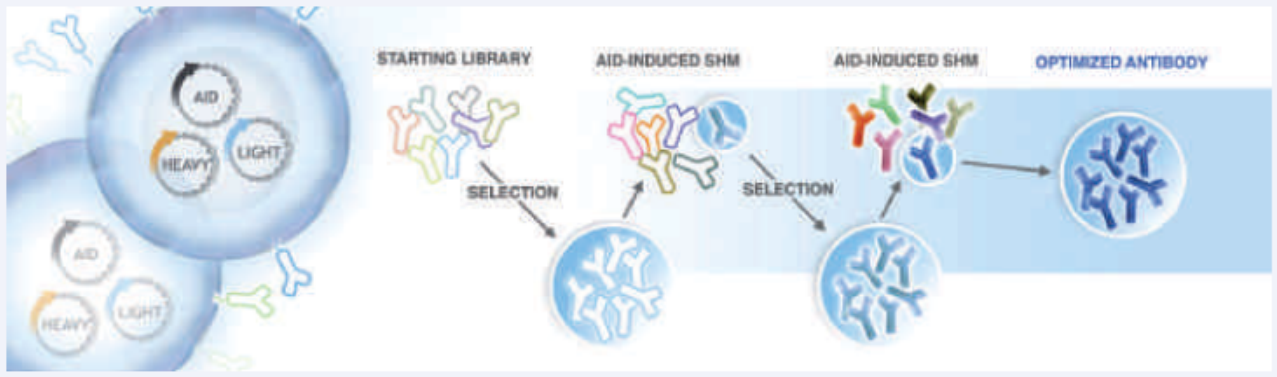

Figure 1. SHM-XEL Ab Discovery Process. Starting with fully-human germline libraries, AnaptysBio utilizes iterative rounds of somatic hypermutation and selection pressure to rapidly generate highly optimized therapeutic antibodies.

By controlling the selective pressure that is applied during SHM, AnaptysBio can simultaneously select antibodies for multiple desirable properties, such as high expression in mammalian cells, dual target binding, high solubility and high stability[5]. Because SHM-XEL uses mAbs in their full-length, natural IgG format, the resulting antibodies are soluble, fully glycosylated and active, allowing cell-based assays and other functional screens to be performed throughout the antibody-generation process[7]. The technology also can be used to humanize antibodies by grafting only the CDR3 loop from a rodent antibody to human frameworks[4,6], which results in a higher degree of homology to the human germline sequence than competing humanization technologies.

Business model

AnaptysBio holds a dominant leadership position in the intellectual property and know-how required to use SHM to discover and optimize therapeutic antibodies. The company is taking a dual approach to value creation: establishing antibody-discovery partnerships and building a proprietary internal pipeline.

Discovery partnerships have permitted AnaptysBio to validate its SHM-XEL platform, generate significant nondilutive funding and establish strategic partnerships with pharmaceutical companies. The company has publicized deals with Roche, Merck, Novartis, Celgene and Gilead. In each of these partnerships, AnaptysBio is responsible for developing therapeutic antibodies through various stages of preclinical development, has received upfront payments and research funding and is eligible for milestones and royalties in exchange for global commercial rights to the delivered antibodies.

The biotech company also has been awarded contracts by two government agencies—the Defense Advanced Research Projects Agency and the Defense Threat Reduction Agency—to generate thermally stable mAbs against biowarfare agents for various biodefense purposes.

For its internal pipeline, AnaptysBio is focusing on five disease areas: cancer immunotherapy, muscle-wasting disorders, pustular psoriasis, atopic dermatitis and fibrosis. In cancer immunotherapy, the company aims to upregulate the immune system by blocking multiple negative regulators of T cell function, including PD-1, TIM-3 and LAG-3. By modulating multiple targets with a combination of mAbs or a single antibody that can block multiple targets, AnaptysBio aims to treat solid tumor indications such as non–small lung cancer, renal cell carcinoma and melanoma. The lead antibody in this program, ANB011, blocks the interaction between PD-1 and PD-L1 and is in preclinical development.

AnaptysBio has successfully generated a highly potent activin type II receptor (ActRIIB) antibody, called ANB012, and it is currently in preclinical *in vivo* testing. ANB012 is intended to treat various muscle-wasting disorders, such as cancer cachexia, AIDS-related cachexia and post-surgical muscle loss. AnaptysBio is also actively developing therapeutic antibodies against emerging targets in pustular psoriasis, atopic dermatitis and fibrosis.

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