Crystal Bioscience Inc.

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Exceptional antibodies from a new technology

Crystal Bioscience's unique antibody discovery platform exploits the benefit of employing a species that is phylogenetically distant from humans for the purpose of antibody discovery coupled with the company's proprietary gel-encapsulated microenvironment or GEM screening technology

Innovation is the crux of biotechnology and companies introducing new products to the market are shaping the future of the field. Crystal Bioscience is one of those companies. Its scientists are literally hatching a new technology that is helping to unleash the full potential of human antibodies for use in new therapeutics, and may well take the industry in a new direction. First there was the mouse and the rat, and now there is… the chicken.

"We are the only company to make affinity matured, monoclonal antibodies from chickens. In addition, we developed the technology for altering the chicken genome and are applying this knowhow to create our next generation antibody discovery platforms," said Rob Etches, CEO of Crystal Bioscience, based in Emeryville, CA "The unique repertoire in immunized chickens gives us access to epitopes that are unreachable using other animals." More epitopes means more chances of isolating antibodies for developing drugs to fight disease.

Crystal Bioscience's unique platform is built on biological systems of the distant past. "The last common ancestor between chickens and humans was 300 million years ago, compared to that of other mammals at 95 million years ago," explained Etches. That means the chicken host will interpret human target proteins as more foreign than a mouse or rat would, which in turn will trigger a more robust and diverse immune response. "We like to say that the advantage of our system is that it is powered by evolution," said Etches. The greater evolutionary distance between humans and chickens as opposed to mice or rats is clearly apparent in the homology between the host and human DNA sequences. For example, for the HER2 sequence involved in aggressive breast cancer, there is an 88 percent homology between humans and mice versus a 71 percent homology between humans and chickens. A comprehensive list of homology between chicken, human and mouse orthologues on the Crystal Bioscience website (http://www.crystalbioscience.com/homolog2.html) shows that the HER2 example is repeated consistently throughout the genome.

"The company was founded in 2008 to transform the theoretical advantage of accessing the unique antibody repertoire in birds into a robust technology," said Bill Harriman, chief scientific officer at Crystal Bioscience. "As an immunologist, I'm interested in developing more efficient ways to discover useful antibodies, going beyond the traditional species and the traditional methods of recovering monoclonals from them. We know that, immunologically, chickens represent a great host system, but what has held them back in the therapeutics space is the lack of a suitable hybridoma fusion partner, so there has been no way to produce natively paired chicken monoclonal antibodies."

Until now. The team at Crystal Bioscience has circumvented the problem by developing their own GEM, or "gel-encapsulated microenvironment", screening and cloning technology. This is an assay in which antibodies secreted from a single lymphocyte bind to reporter cells or beads. Reporters with different color tags allow Crystal's scientists to identify different antibody activities, which can be evaluated prior to physical cloning. The GEM assay yields selected monoclonal antibodies from a rapid scan of tens of millions of GEMs that are prepared in parallel. Crystal Bioscience induces primary lymphocyte cell cultures into a "plasmablast" phenotype that secretes more antibodies per cell than other B cell stages. "All together, this technology gives us a way to make stable monoclonal antibodies without the huge loss of repertoire associated with cellular fusion. You are going directly from an immunized lymphocyte to a recombinant antibody," Harriman explained. "The ability to ask sophisticated questions during initial screening and recover antibodies with minimal repertoire loss is advantageous for antibody discovery using any host system, but it is especially powerful when applied to a host system that possesses an inherent evolutionary advantage. Since this advantage is driven by the sequence of the human target antigen, it will pertain to our engineered chickens as well."

Crystal's platform has been tested by clients seeking antibodies to elusive targets. "Typically, clients come with antigens that have failed to elicit good antibodies using conventional antibody discovery platforms," explained Harriman. "We typically produce panels of 20 to 100 unique sequence mAbs for clients to select from." The elusive targets that Crystal's technology has addressed range from GPCRs to ion channels to highly conserved proteins. That said, value has been demonstrated in using Crystal's platform for less challenging (that is, more immunogenic) targets as well. "Our clients appreciate the ability to readily acquire mAbs that recognize both the murine and human orthologues," said Harriman. These cross-reactive antibodies simplify early stages of the therapeutic discovery process when murine models are used to acquire preclinical data.

Genetically engineered chickens for antibody discovery are the wave of the future for Crystal Bioscience. The ultimate goal in therapeutic antibody discovery programs is identification of fully human, biologically active, high affinity antibodies, and the "SynV Chicken" is the newest tool to make it happen. Like its predecessors of mammalian origin, the SynV chicken produces fully human antibodies. The team at Crystal Bioscience has created a knockout chicken using classical targeting constructs with regions of homology located 5' and 3' of the IgH and IgL loci. They have also inserted a synthetic V region with different attributes to foster a robust immune response to yield best-in-class fully human antibodies. "This is the first time anyone has knocked out the IgH gene in chickens and it is a key part of our IP portfolio," said Etches. "It was a herculean task to sequence the IgH locus, knock it out, and show that it is genetically correct with the expected phenotype."

Harriman agrees this is a huge breakthrough. "We have, in essence, the key to a very special genomic location, and we can precisely insert genes of interest into it. This is a highly specialized locus that has evolved over millions of years to create diversity in a highly specialized cell type capable of amplifying rare desirable events through a complex in vivo antigen-driven selection process," he said.

Meanwhile, Crystal Bioscience is poised to start licensing its SynV Chicken platform alongside its GEM assay, which is available now. Harriman expects that companies currently using other transgenic animals will want to see the added benefit of the SynV Chicken. Alternatively, companies that are late to enter the therapeutic antibody space may see this as an opportunity to leapfrog others that have already invested in competing technologies. Harriman adds that Crystal Bioscience is interested in developing over time a suite of novel transgenic assets based upon immunoglobulin and other scaffolds, and hopes to join forces with pharmaceutical companies interested in capitalizing on their products. As he said, "A company that partners with us will be doing groundbreaking work."

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