IN brief

Farmer threat to Monsanto recedes

Farmer Vernon Bowman.

The US Supreme Court heard on February 19 oral arguments in *Bowman v. Monsanto Co.*, the outcome of which will have implications for selfreplicating products and the broader biotech industry. The lawsuit pits US farmer Vernon Bowman against St. Louis–based Monsanto over the farmer's apparent attempt to circumvent the patent on the agbiotech giant's herbicide-resistant Roundup Ready seeds. The Indiana farmer bought Roundup Ready soya and harvested a first crop; he later purchased seed from a grain elevator, most often purchased for animal feed, under the assumption that the mix of seeds might contain some that were genetically modified. He argued that using these next-generation seeds for a second crop was legal in light of the doctrine of patent exhaustion, which states that patented inventions can be sold only once, and that Monsanto's patent on the seeds he used had run out by the time he planted them. Monsanto took Bowman to court and Bowman was ordered to pay $84,000. Bowman appealed, but the Court of Appeals for the Federal Circuit upheld the district court's decision that Bowman had infringed Monsanto's patents. Intellectual property professionals were surprised when the Supreme Court agreed to hear the case in the face of Obama administration requests that it let lower-court rulings stand. More is at stake than transgenic plants and seeds, explains William Simmons at Sughrue Mion law firm in Washington, DC. "Some of the patent claims are directed to DNAs, genetic constructs and vectors—materials that almost every university or biotech company commonly uses, develops and sometimes patents." An *amicus* brief filed by a group of major universities and technology transfer offices urges the Court to affirm the Federal Circuit decision. "A poor decision in the case could adversely impact the industry at large," says Simmons. "For example, if the Court decides that a first sale of a single copy of a patented RNA construct exhausts the patent owner's rights to that construct, the single copy could be easily used to create an infinite number of copies of the RNA without any recourse by the patent owner. In other words, the Court would make it necessary for the patent owner to recover all of the costs of the research and development in the biotech immediately, in the first sale of it, which could make it unaffordable for many." The Court's decision is expected in a few months.

Michael Francisco

tions on what targets the mice are deployed against. CEO Andy Sandham says these licenses were drawn up after discussions with potential partners about how they would like to use the technology.

In addition, Kymab has set up a separate company, Kymab Access, to allow academics to use its technology. The idea is to form collaborations with groups that are experts in the biology of specific diseases, with Kymab generating antibodies against targets they provide. Unlike Ablexis, Kymab has only one backer, the investment division of the research charity the London-based Wellcome Trust, which put in £20 ($30.2) million at the foundation of the company in 2009. Mark Walport, director of the trust, says Wellcome is "committed to realizing the broad application of [Kymab's] technology" to treat rare and neglected diseases.

Just after the launch of Kymouse HK, Merus announced it had completed validation of its transgenic MeMo mouse, engineered to generate antibodies with a single human common light chain and diverse human heavy chains. The MeMo mouse contains a single human V gene light chain under the control of genetic elements that drive B cell–specific expression, and which reduces the level of somatic hypermutations in the light chain but not in the heavy chain.

The company spent the previous year immunizing MeMo mice with half a dozen antigens and analyzing the immune responses. According to COO Mark Throsby, "Serum antibody titers, and size, diversity, functionality and developability of antibody panels are comparable to those of wild-type mice."

The single human light chain drives the generation of a normal B-cell compartment and supports a robust immune response. Because of the common light chain, MeMo-derived antibodies can be expressed and assembled in a single clonal cell. This allows them to generate bispecific antibodies rapidly (Merus calls these biclonics) and combinations of antibodies (dubbed oligoclonics by Merus). The MeMo mouse is now available for licensing.

Around the same time, the first fully engineered Crescendo mouse was born, in September 2012. Mike Romanos, CEO of Crescendo, is adamant that the company's technology is neither a successor to nor a sibling of all the other mouse platforms. Instead, he is positioning the Crescendo mouse as the direct descendent of Ablynx's Nanobody platform. Nanobodies consist of single domain, V_H fragments, which are generated naturally in llamas. The Crescendo mouse—claimed as the world's first triple knockout—produces human V_H fragments (with no associated light chains), so that unlike those derived from llamas, there is no need for subsequent humanization. Romanos claims Crescendo will be able to halve the discovery phase, going from immunizing a mouse to delivering a candidate V_H fragment in six months.

As the smallest antibody fragments that bind to an antigen, these V_H fragments are expected to broaden the field of targets that can be modulated by antibodies. Targets could include G protein–coupled receptor and ion channels, for example. They also promise to be amenable to bi- or multispecific formats and easy to manufacture in microbial systems.

The Crescendo mouse is the invention of Marianne Brüggemann, another veteran of the *in vivo* platform scene, who was the first to demonstrate it is possible to generate transgenic mice with elements of the human humoral immune system, the technology that underpins both HuMAb-mouse and XenoMouse. Crescendo intends to license its mouse and is also using it to generate an in-house portfolio.

It's curious that the company one would expect to view itself as successor to Ablynx, in fact sees itself in direct competition with the transgenic mouse platforms. arGEN-X, set up by former Ablynx executives is also using llamas as the source of antibodies. But unlike Ablynx, arGEN-X is generating complete antibodies. As CEO Tim Van Hauwermeiren explains, llamas have two types of antibodies in their immune repertoire: heavy chain only, which are the starting point for Ablynx's nanobodies, and conventional antibodies that have human-like variable regions.

"All human antibody germlines appear in llama and are used with the same frequency," Van Hauwermeiren says. "The sequence of these variable regions is as homologous to human germline as variable regions of transgenic mice." What sets llamas apart from humans and mice is that the llama sequence of a disease target is quite different. "This explains the strong and diverse immune response we typically see upon immunization with human disease targets," says Van Hauwermeiren. The diversity obtained from two to four llamas is greater than immunizing hundreds of transgenic mice, he claims.

This capability played out in a project conducted with Eli Lilly, of Indianapolis. arGEN-X generated more than a dozen unique antibodies, all hitting the desired epitope, whereas Lilly's in-house mouse platforms and phage libraries failed to come up with a single suitable antibody.

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