Kymab Ltd.

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Kymouse: the 100-trillion antibody mouse

Kymab's groundbreaking transgenic mouse platform, with its library of 100-trillion antibodies and natural ability to optimize leads *in vivo*, is transforming human monoclonal antibody discovery.

Kymab's Cambridge-based team of industry leaders is laying the foundation to build a significant R&D company by exploiting the power of its industry-beating technology. Both the Wellcome Trust and the Bill and Melinda Gates Foundation—two of the world's largest healthcare foundations—have invested over $70 million to enable the company to realize its long-term vision and create a world-class pipeline of fully human monoclonal antibodies (mAbs) and vaccines. To complement this strategy, Kymab is entering into a limited number of strategic alliances to strengthen the drug pipelines of industrial partners. Big pharma has already drawn upon the power of Kymab's technology, with Novo Nordisk striking a deal with Kymab in a partnership that generated leads for Novo's programs.

mAbs are one of the best-selling classes of drugs today, largely because of their excellent efficacy and safety profiles. Although fully human antibodies can be generated using phage display or transgenic animal platforms, both approaches have historically had their drawbacks. Despite the billions of dollars and intensive R&D focused on phage display over the last 25 years, only 3 antibodies—Humira, Benlysta and Cyramza—have made it to the market, with an additional 5 in phase 3 trials. Over a similar time frame, mouse platforms have produced 7 marketed, fully human antibodies, and 13 are in phase 3 (**Table 1**).

Despite their success, some transgenic mouse platforms have been engineered in ways that limit their performance in the discovery of therapeutic mAbs and vaccines. Kymab has designed and engineered mice that expand those limits, resulting in a discovery platform with exceptional performance. Of note, Kymouse is engineered to contain the entire repertoire of human immunoglobulin variable genes, the only humanized murine discovery platform to do so. The genes have been inserted precisely into the corresponding locations within the mouse genome rather than by random integration, and no murine DNA has been deleted. In addition, large genomic inversions provide a means to eliminate the incorporation of mouse variable sequences while retaining genes essential for the normal physiology of the mice. These design features deliver fertile, phenotypically normal mice that breed, elicit typical immune responses and generate therapeutic human mAbs.

"The performance we are seeing with the Kymouse platform is extraordinary," said David Chiswell, chairman at Kymab and the founding CEO of Cambridge Antibody Technology (acquired by AstraZeneca in 2006). "The potential to identify functional antibodies to validated targets where other platforms have failed positions Kymab, and its partners, way ahead of the competition."

Designed by Jerico Santander on behalf of Kymab Ltd.

The Kymouse discovery platform is designed to contain the entire diversity of the human antibody gene repertoire. The platform rapidly generates diverse panels of high affinity functional antibodies that require no lead optimization because molecules are affinity matured *in vivo* by the mouse.

Antibodies isolated using Kymouse are essentially ready to be developed as drugs and do not require iterative rounds of engineering. From its 100-trillion antibody library, the platform rapidly generates very high-affinity, candidate-quality molecules without the need for lead optimization; the candidates are optimized *in vivo* and can be selected based on the desired potency, mechanism of action, species cross-reactivity and biophysical properties. "After identifying a drug target with interesting biology, we can select a candidate molecule in less than 18 months to take into development," explained Chiswell.

Published in *Nature Biotechnology*, Kymab's feat is the most ambitious humanization

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project of the mouse genome ever undertaken. The peer-reviewed paper is the first to describe transgenic mice with a complete human antibody repertoire, and it details the insertion of 5.4-million bases of human DNA, representing 0.1% of the human genome[1].

Another major application of the technology lies in the potential of the mice to generate an antibody response that closely resembles the human response. One of the aims of vaccine R&D is to discover immunogens able to elicit broadly neutralizing antibodies against clinically important pathogens, such as respiratory syncytial virus, influenza virus and HIV. Thus, the Kymouse technology platform can greatly facilitate selection of the right vaccine candidates based on their ability to induce neutralizing antibody profiles similar to those observed in infected humans, making vaccine antigen selection predictive. This aspect of the technology has compelled the Bill and Melinda Gates Foundation to invest heavily in the company and engage Kymab on vaccine antigen discovery R&D, initially on malaria.

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To further accelerate and improve the discovery and development process, the Kymab team has two additional technologies up its sleeve. To support the development of predictive disease models in mice or to overcome human targets that are highly homologous to murine sequences, Kymab is able to rapidly create gene knockouts and knock-ins in the Kymouse strains. This enhances the company's ability to generate antibodies that are directed to highly conserved and functionally important epitopes and are cross-reactive between species, which facilitates preclinical studies. This is complemented by a rapid B cell screening technology, which deeply mines the Kymouse library to isolate the rare, candidate-quality molecules that may otherwise be lost by the older, extremely inefficient hybridoma technique.

The Kymab team has the technology, investment and decades of commercial experience in discovery and development to deliver human mAb therapeutics to the clinic. The company has an internal pipeline of 10 programs and is expected to become a clinical stage biopharmaceutical company by 2016. Founded in 2009 by Professor Allan Bradley FRS, Kymab is the first spin-out company from the Wellcome Trust Sanger Institute, a world-leading genomics research center. Kymab is a founding partner of the newly established Cambridge Institute of Therapeutic Immunology and Infectious Disease, alongside AstraZeneca, GlaxoSmithKline, UCB Celltech and the Wellcome Trust. It also has an academic access program to collaborate with leading experts interested in translating their research from the bench to the clinic (www.kymabaccess.org).

Kymab is exploring collaborations to exploit its discovery and development capability to fuel the pipelines of big pharma. Its core areas of therapeutic interest are oncology, immuno-oncology and autoimmunity, but it is open to discussions on targets across other disease areas.

Table 1. Fully human antibody products on the market or in phase 3 trials.

Brand name	Non proprietary name	Status	Company	Platform
Ilaris	canakinumab	Market	Novartis	Mouse
Prolia & Xgeva	denosumab	Market	Amgen	Mouse
Simponi	golimumab	Market	Johnson & Johnson	Mouse
Yervoy	ipilimumab	Market	Bristol-Myers Squibb	Mouse
Arzerra	ofatumumab	Market	Genmab/GlaxoSmithKline	Mouse
Vectibix	panitumumab	Market	Amgen	Mouse
Stelara	ustekinumab	Market	Johnson & Johnson	Mouse
Cyramza	ramucirumab	Market	Eli Lilly	Phage
Humira	adalimumab	Market	AbbVie	Phage
Benlysta	belimumab	Market	GlaxoSmithKline	Phage
Opdivo	nivolumab	Phase 3	Bristol-Myers Squibb	Mouse
	secukinumab	Phase 3	Novartis	Mouse
	evolocumab	Phase 3	Amgen	Mouse
	alirocumab	Phase 3	Regeneron/Sanofi	Mouse
	dupilumab	Phase 3	Regeneron/Sanofi	Mouse
	SII RMab	Phase 3	Serum Institute of India	Mouse
	brodalumab	Phase 3	AstraZeneca	Mouse
	sarilumab	Phase 3	Regeneron/Sanofi	Mouse
	tabalumab	Phase 3	Eli Lilly	Mouse
	actoxumab + bezlotoxumab	Phase 3	Merck	Mouse
	daratumumab	Phase 3	Johnson & Johnson	Mouse
	rilotumumab	Phase 3	Amgen	Mouse
	patritumab	Phase 3	Daiichi Sankyo	Mouse
	necitumumab	Phase 3	Eli Lilly	Phage
	tralokinumab	Phase 3	MedImmune	Phage
	briakinumab	Phase 3	Abbott	Phage
	gantenerumab	Phase 3	Roche	Phage
	bimagrumab	Phase 3	Novartis	Phage

References

1. Lee, E.C. *et al. Nat. Biotechnol.* **32**, 356–363 (2014).

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