Innovative Targeting Solutions, Inc.

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First-in-class, breakthrough protein-engineering platform tackles tough targets

Innovative Targeting Solutions' mammalian display antibody-generating platform, HuTARG, is a unique tool for direct *de novo* generation of extensive panels of high-affinity, fully human antibodies and their simultaneous functional screening at the single-cell level.

The efficient generation of functional, fully human antibodies against traditionally difficult targets such as G protein–coupled receptors has been hampered by the proteins' inaccessibility in their native context and technical complexities associated with antibodies in non-native *in vitro* and *in vivo* systems[1]. Innovative Targeting Solutions (ITS) has recently shown, however, that it can surmount these challenges using its *in vitro*–based, V(D)J recombination mammalian display antibody-generation platform called HuTARG.

ITS has not only been able to generate two first-in-class agonist antibodies, one to the glucagon-like peptide-1 or GLP1 receptor and one to the glucagon receptor, and a first-in-class antagonist antibody to the parathyroid hormone receptor, but also it is now applying HuTARG to generate a dual agonist to the GLP1 and glucagon receptors as well as a heavy chain–only antibody to human CD3.

ITS is currently seeking opportunities to license HuTARG technology to companies looking to streamline and improve their own antibody-generation capabilities. Founded in 2008 by Michael Gallo, former VP of Abgenix and member of the team that created XenoMouse[2], ITS harnesses nature's most powerful diversity-generating system, V(D)J recombination, for the *de novo* creation of fully human antibody libraries of 10^9 or greater variants in a mammalian format. Because HuTARG is a mammalian display platform, with each cell expressing a unique antibody, it allows for the straightforward functional screening of billions of fully human antibodies in a single day. This is a first for the industry and opens the doors to tackling a number of targets previously considered very hard or even impossible to modulate.

What makes the technology a real breakthrough is that the generation of these vast repertoires does not require the manipulation of large recombinant libraries. "It takes people a moment to appreciate how revolutionary this is. No cloning and no transformations—the cell does all the work to generate repertoires at your scale of choice. Scientists love it, and I personally cannot see an easier way to generate antibodies. Cells are expanded to the numbers desired, V(D)J recombination is induced and *de novo* diversity is generated *in vitro*," said ITS president Michael Gallo.

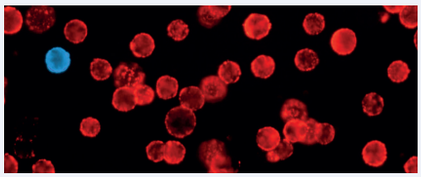
HuTARG overcomes the principal bottlenecks that have hindered mammalian display from being widely adapted for drug discovery. The full potential to generate large cell libraries, engineer full-length native scaffolds and assay for function in a single-cell context is now possible, resulting in ITS generating the world's first functional peptide-grafted agonist antibodies against the GLP1 and glucagon receptors. HuTARG has several key components that contribute to its robustness and versatility. First, ITS researchers harnessed nature's way of generating virtually limitless antibody variants by adopting V(D)J recombination, the process responsible for the large repertoire of binding specificities in B cells and T cells, as the diversity-generating engine for HuTARG.

The team further finessed nature's diversity-generation machinery to target mutations exclusively to the complementarity-determining regions (CDRs), leaving framework regions in their native germline configuration and thus circumventing the need to reverse-engineer antibodies as is required with phage- or yeast-based platforms. Because affinity maturation takes place in a mammalian display format, the approach allows isolation of high-affinity variants that are highly expressed, thereby ensuring optimal manufacturability.

In addition to *de novo* antibody generation and affinity maturation, the platform's versatility lends itself to other unique applications. Because V(D)J recombination simultaneously generates diversity in the length and composition of junctions at CDR3, and because HuTARG utilizes the complete human VH and JH repertories, the technology makes it possible to graft sequences encoding functional peptides into the CDRs of the full-length IgG scaffold. ITS has successfully applied this approach to generate both agonist and antagonist antibodies to three different G protein–coupled receptors. Grafting of peptides into the full-length human antibody scaffold not only protects the peptide from proteolytic processing but also imparts the long serum half-life of an antibody, resulting in a biologic that combines the best features of both modalities.

ITS is already exploiting the versatility of HuTARG to develop its own pipeline with an intriguing set of first-in-class molecules. First in line is the development of antibodies bearing multiple specificities—dual agonists to the GLP1 and glucagon receptors. ITS will be presenting data on these molecules at the 2014 Antibody Engineering Conference in Huntington Beach, California, and is looking for a partner to advance these assets.

Another significant adaptation of HuTARG is its use for the generation of heavy chain–only antibodies (HCAbs). This application brings the specificity, efficiency and manufacturability of the platform to the generation of a structurally simpler and thus therapeutically more modular antibody format for drug discovery. HCAbs are being widely embraced by the pharmaceutical community, and HuTARG provides substantial advantages over all other platforms currently in use for generating HCAbs. ITS is currently developing an antihuman CD3 HCAb to be used for T cell recruitment applications.



Innovative Targeting Solutions' HuTARG platform allows for the functional screening of de novo-created, fully human antibody libraries of greater than 10^9 variants and the isolation of rare antibodies with the desired properties by flow cytometry.

ITS recently extended a research collaboration with Amgen, through which the pharmaceutical company is entitled to internalize the HuTARG platform, and is in discussions with several other pharmaceutical companies interested in applying the technology to their internal drug discovery efforts. HuTARG is much more than an antibody-generation technology—it is a protein-engineering platform that can be applied to direct specificity, alter affinity or improve expression of antibodies, non-Ig scaffolds or peptides.

With the development of biologics growing exponentially, this tool will no doubt contribute to the successful engineering of future therapeutics. ITS feels that there are no limits to what the technology can discover. Already in active research is a suite of peptide-grafted venom peptides to generate functional antibodies to ion channels.

References

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