

## Unlocking the potential of ion channel biologics

**TetraGenetics' breakthrough technology produces unprecedented levels of correctly folded and functional membrane-spanning proteins that enable the discovery of novel therapeutic antibodies.**

Ion channel proteins are found on all cell types and allow the passage of ions across cellular membranes. They are involved in a wide variety of biological processes and are implicated in many pathological conditions including cardiopathies, autoimmune disease, epilepsy, anxiety, depression, cancer and pain. The fact that only 8% of all ion channels are targeted by 18% of small-molecule drugs listed in the ChEMBL database<sup>1</sup> highlights the significant number of therapeutic opportunities that remain unexplored.

Nearly all ion-channel-targeting drugs on the market are small molecules, many of which were developed long before their molecular targets were identified. Advances in patch clamp technology and, more recently, cryo-electron microscopy have helped researchers characterize the physiological function and structure of ion channels. However, despite an explosion in ion channel drug discovery programs, their efforts have been disappointing, with only 13 new ion-channel-targeting drugs approved in the past 10 years.

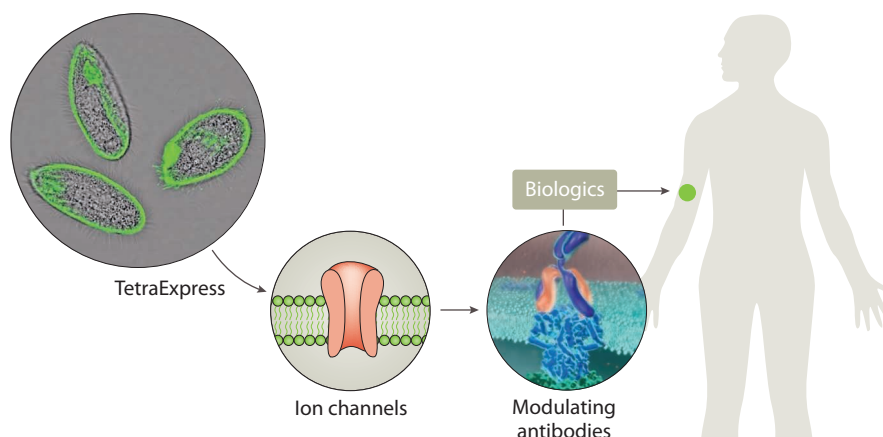
Although the genes encoding ion channels tend to be highly conserved among family members, closely related channels can have distinct physiological properties, which makes it challenging, and critically important, to develop selective and safe molecules that perturb their function.

"The problem of selectivity has turned the industry's attention towards discovering and developing therapeutic antibodies targeting ion channels," explained Paul Colussi, VP of research at the US-based biotech company TetraGenetics. "Such antibodies offer a novel, more selective and thus safer approach for treating ion-channel-related diseases," he added.

Antibodies are also more versatile than small molecules—they can be engineered to modulate channel activity in different ways, exert immunomodulatory functions or be conjugated to cytotoxic drugs—and can have more favorable pharmacokinetic and pharmacodynamic properties. Thus far, one antibody (BIL010t; Biosceptre) that targets a nonfunctional form of the ligand-gated ion channel P2X purinoceptor 7 has reached clinical trials for the treatment of basal cell carcinoma. Yet, this number is set to grow owing to improvements in two areas, namely, the production of ion channel targets that can be formulated as either potent antigens or antibody-screening tools, and the use of antibody discovery platforms that enable the identification of rare functional antibodies.

### Enhancing ion channel production

"Ion channels are notoriously difficult to express in standard cell lines and producing enough of them to launch therapeutic antibody discovery campaigns can be challenging," said Ted Clark, founder of TetraGenetics and professor of microbiology and immunology at Cornell University.



**Fig. 1 | Antibody discovery using TetraExpress technology.**

TetraGenetics' proprietary TetraExpress system relies on the free-living ciliate *Tetrahymena thermophila*, which has the ability to produce 100 times more correctly folded and functional ion channel protein than other systems, enabling antibody discovery against these intractable targets (Fig. 1).

In addition to its short life cycle and cost-effective laboratory handling, the metabolism of *T. thermophila*, which is geared toward membrane protein expression, and its post-translational machinery, which supports the addition of mammalian-like post-translational modifications, make it an ideal expression system for recombinant ion channels.

"By using the TetraExpress system and our optimized expression and purification approaches, we can obtain multiple milligrams of conformationally relevant purified protein," Clark explained.

### Unique formulations

To enable antibody discovery, membrane protein scientists at TetraGenetics encapsulate and stabilize purified protein in an artificial bilayer with immunostimulating molecules to generate adjuvanted proteoliposomes that can be injected into host animals. For antibody-screening purposes, purified ion channels are immobilized on a solid support (typically a bead format) and stabilized in a lipid bilayer. In the latter formulation, ensuring that the surface of the ion channel is exposed to the antibodies is key.

As Clark said, "unlike other membrane proteins, including GPCRs [G protein-coupled receptors], which have large portions dangling outside the membrane available for antibody recognition and binding, for many important ion channel targets most of the protein is inside the cell and there is only a tiny portion sticking outside the cell that is available to react with antibodies."

The ability to access large amounts of ion channel protein allows TetraGenetics to customize their formulations to any antibody platform. "This has been a real advantage, giving us multiple shots on goal with different systems to produce antibodies as well as screening tools," he added.

### Advancing therapeutic antibody development

With ten ion channel drug discovery programs in its pipeline, TetraGenetics is working with other biotech companies, leading universities, foundations and government agencies to develop therapeutic antibodies.

TetraGenetics' technology has already enabled the identification of functional antibodies that target several ion channels implicated in autoimmune and respiratory diseases (Kv1.3 and KCa3.1). "Our most advanced candidate is set to enter clinical trials in the first quarter of 2021," said Colussi.

Future research on ion channels involved in respiratory disease, cancer and central nervous system disorders will potentially lead to novel antibody drugs for a huge range of diseases. TetraGenetics is seeking to establish new strategic partnerships with pharmaceutical companies working on antibody discovery and development to unlock the potential of ion channel therapeutics.

1. Santos, R. et al. *Nat. Rev. Drug Discov.* **16**, 19–34 (2017).

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