Light Chain Bioscience
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LIGHTCHAIN BIOSCIENCE

Next-generation immunotherapy with native bispecific antibodies

Light Chain Bioscience is leveraging its proprietary bispecific antibody format to advance immune therapies in oncology and beyond

The Swiss biopharmaceutical company Light Chain Bioscience has developed a novel and unique class of human, bispecific antibodies dubbed κλ bodies, so-called because they combine a κ light chain that recognizes a first target and a λ light chain that recognizes a second one, into a native human antibody structure. In collaboration with TG Therapeutics, Light Chain has brought one internally developed κλ body, TG-1801 (formerly NI-1701), into clinical trials for relapsed/refractory B cell lymphoma, and has a number of others in the pipeline for the treatment of various tumors and blood disorders.

Light Chain emerged from Novimmune, which over the past 20 years has developed monoclonal antibodies (mAbs) in inflammatory and autoimmune diseases, with seven reaching clinical trials and one, the anti-interferon mAb Gamifant (emapalumab), gaining approval by the US Food and Drug Administration (FDA) in 2018 as the first treatment for hemophagocytic lymphohistiocytosis. In July 2019, Novimmune divested Gamifant and related activities, and rebranded as Light Chain Bioscience with a focus on bispecific antibodies. Light Chain, which draws on decades of experience in immunology and antibody-based therapies gained as Novimmune, is now seeking partners to take forward candidates identified by Light Chain, as well as partners seeking to apply Light Chain's expertise and technology platform to their own projects.

"Building on Novimmune's long experience in antibody discovery and development, Light Chain Bioscience now focuses on leveraging the unique features of its bispecific antibody format", said Erich Hunziker, Chairman of Light Chain Bioscience.

Bispecific antibodies represent a rapidly growing therapeutic approach, and many methods have been devised for their production. Often this has required extensive engineering of antibodies at their interfaces, or addition of linkers and other foreign sequences, to facilitate assembly and allow the cells expressing the antibodies to produce the bispecific product in sufficient quantities.

Light Chain's approach is different, creating bispecific antibodies that are essentially fully human, with no engineering required. The method for creating bispecific κλ bodies is simple: a production cell expresses a single heavy chain, alongside κ and λ light chains, which self-assemble into functional antibodies. This process creates a mixture of antibodies, 25% of which are monospecific containing two κ identical chains, 25% are monospecific with two identical λ chains and 50% are bispecific κλ bodies, which can be very effectively purified from the supernatant using affinity reagents binding to the two different light chains.

Light Chain's bispecific platform not only bypasses engineering challenges but also offers a simple and scalable manufacturing process. Working with contract manufacturing company Lonza Pharma & Biotech, Light Chain has already manufactured κλ bodies under good manufacturing practice (GMP) on a 1,000-litre scale in several runs, with high yields (Fig. 1).

As more and more bispecific antibodies have entered clinical trials, immunogenicity potentially associated with engineered or foreign elements in the antibodies is emerging as a significant concern. Light Chain's κλ bodies have no modifications, except for the loops present in the extremities of the light chains that create the desired target specificity, as in any normal human antibody.

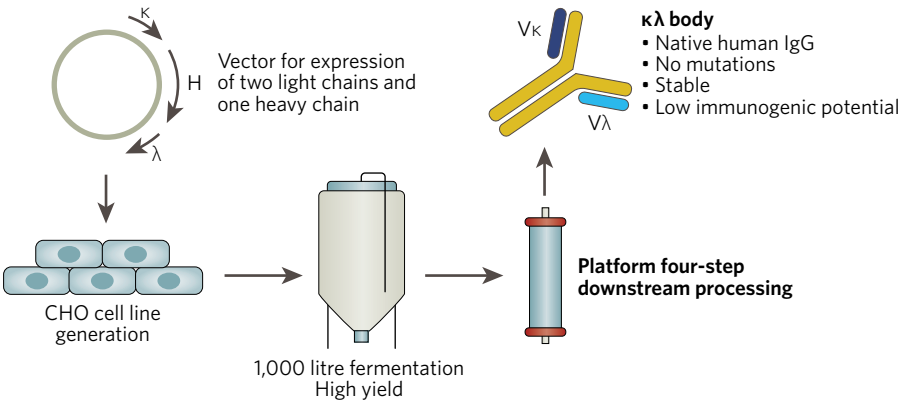

Fig. 1 | κλ body production process. Simple co-expression and assembly of two light chains and one heavy chain in stably transfected Chinese Hamster ovary (CHO) cells, followed by a downstream purification process applicable to any κλ body. The final product is a bispecific antibody fully retaining the native structure of a human IgG.

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"Over the last decade challenges linked to bispecific antibodies engineering and manufacturing have been overcome. The field is now beginning to face the issue of immunogenicity," said Nicolas Fischer, CEO of Light Chain Bioscience. "The native structure of κλ bodies is likely to represent a significant advantage."

Targeting innate immune checkpoints

Light Chain's most advanced bispecific κλ body candidate is TG-1801, which has binding moieties for CD47 and the B cell surface antigen CD19, and is in phase 1 trials for relapsed/refractory B cell lymphoma. CD47 is an immune checkpoint protein that functions as a regulator of phagocytosis. Cancer immunotherapies that target adaptive immune checkpoints have demonstrated clinical benefits in a range of cancers, and in recent years the idea of targeting innate immune checkpoints has emerged as a hot topic, with CD47 widely seen as an exciting new innate checkpoint molecule.

CD47 is a membrane-bound protein expressed on tumor cells, as well as all normal cells in the body, where it acts as a 'don't eat me!' signal. CD47 communicates this message by binding to signal-regulatory protein-α (SIRPα) on phagocytic cells, particularly macrophages; this binding in turn inhibits phagocytosis.

Tumor cells frequently hijack this system and overexpress CD47, which translates clinically into worse prognoses across several cancer indications. Blocking the signalling between CD47 and SIRPα with anti-CD47 mAbs increases the phagocytosis and killing of tumor cells. However, early examples of this approach contained a fully functional

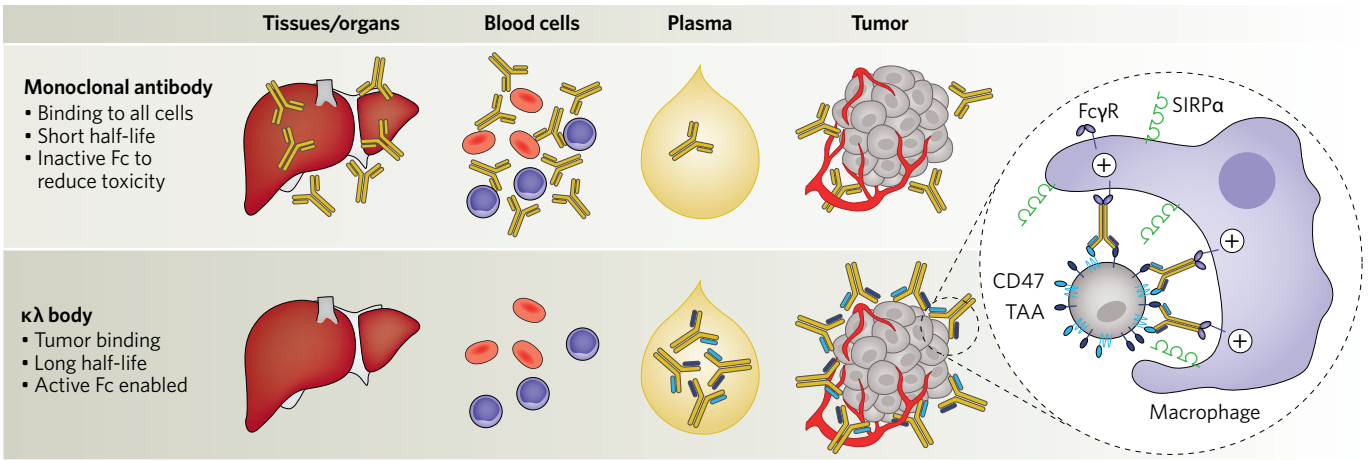

Fig. 2 | Selective CD47 targeting using κλ bodies. Anti-CD47 monoclonal antibodies bind to CD47 expressed on cells in blood and tissues. Ubiquitous binding leads to reduced plasma concentrations of free drug able to reach the tumor (top panel). Bispecific κλ bodies bind only to cells expressing a selected tumor-associated antigen (TAA) and will then co-engage CD47 on their surface. Blockade of the CD47-mediated 'don't eat me signal', combined with FcγR engagement via an active Fc, enhances tumor destruction by phagocytes (lower panel). SIRPα, signal-regulatory protein-α.

Fc portion that led to indiscriminate binding and killing of normal cells, including red blood cells (RBCs) and platelets, which resulted in dangerous thrombocytopenia.

To overcome the challenge of hemotoxicity, anti-CD47 mAbs that carry a silenced Fc portion have been developed, but these have to be administered alongside a second mAb directed against a tumor-associated antigen (TAA) such as HER2 (also known as ERBB2), CD19 or CD20. Light Chain's TG-1801 combines the functions of two antibodies, with one light chain binding to CD47 and the other to CD19.

The CD47-binding domain has been optimized so that it binds with relatively low affinity, which ensures that it does not remain bound to normal cells, including RBCs and platelets. The CD19-binding domain, however, binds to its ligand tightly and anchors TG-1801 on the surface of B cells, where it can then co-bind to CD47. Because TG-1801 only binds strongly to CD47 in the presence of CD19 on B cells, it is able to retain a fully functional Fc portion without causing hemotoxicity (Fig. 2).

Crucially, because the Fc portion is fully functional in TG-1801, it can recruit macrophages as well as other effector cells in the tumor microenvironment to eat and kill tumor cells that they would otherwise ignore. Studies with non-human primates have shown that in a model system in which CD47 is ubiquitously expressed, TG-1801 has good pharmacokinetic properties and does not cause hemotoxicity. TG-1801 is being jointly developed with TG Therapeutics and is currently in a phase 1 trial for B cell lymphoma.

TG-1801 established proof of principle for the bispecific κλ body approach, and Light Chain has six other bispecific candidates coming through the pipeline, developed internally or in collaboration with partners. NI-1801, a follow-on molecule, also contains a CD47-binding light chain and has the same mechanism of action as TG-1801. However, instead of co-binding with CD19, NI-1801 binds to mesothelin. Light Chain anticipates that NI-1801, which is being developed to target a range of solid tumors, will be ready to enter the clinic in 2021. In addition, Light Chain has developed candidates for indications beyond oncology, including NI-2101 for Takeda, which targets factor IX and factor X for the treatment of hemophilia.

> **"Our dual targeting strategy has the potential of combining CD47 inhibition with an improved safety and pharmacokinetic profile, allowing for more drug to reach and target the tumor**
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> Walter Ferlin, CSO, Light Chain Bioscience

"Emerging clinical data put CD47 under the spotlight. Our dual targeting strategy has the potential of combining CD47 inhibition with an improved safety and pharmacokinetic profile, allowing for more drug to reach and target the tumor," said Walter Ferlin, CSO of Light Chain Bioscience.

Light Chain is also developing T cell retargeting therapies using bispecific antibodies. This approach was first validated by the approval of Blincyto (blinatumomab; Amgen) for the treatment of refractory acute lymphoblastic leukemia. Since then, T cell retargeting has been widely developed and represents one of the main applications of bispecific antibodies in oncology. This mechanism of action can readily be achieved with κλ bodies and several programs are being developed with partners for the treatment of solid cancers.

Beyond bispecifics

Looking into the future, Light Chain is leveraging a feature of its technology platform that enables the production from a single cell of well-controlled mixtures of monospecific and/or bispecific antibodies. Subsets composed of a few bispecific antibodies can be readily purified using affinity chromatography. The combination of therapeutic modalities is clearly the way forward to achieve responses in cancer patients. As more and more combinations of antibodies are being developed to treat complex diseases, the generation of a product consisting of several mono- or bispecific antibodies represents an attractive possibility for next-generation therapeutics.

Today Light Chain seeks partners to work on projects in immuno-oncology and other therapeutic areas. Light Chain would like to hear from companies with the skills and expertise to co-develop internally discovered candidates such as NI-1801 and take them into the clinical stages of development. In addition, Light Chain welcomes discussions with prospective partners who want to draw on Light Chain's deep well of expertise in bispecific antibodies for CD47 targeting and T cell retargeting, as well as other approaches outside oncology.

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