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The impact of CAR T cell patenting on access to therapy in Canada

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Typically, when launching a new therapy, such as a drug or biologic, the sponsor of the therapy attempts to obtain broad patent protection to prevent others from launching a similar, competing therapy. But what happens when that broad protection is not obtainable, and the therapy is not a drug at all? These are the questions that sponsors of CAR T cell therapy are grappling with after a recent U.S. patent decision providing narrow patent scope for a basic CAR T therapy patent. This Update examines that decision and potential implications for CAR T cell therapy patent protection in Canada.

On August 26, 2021, in *Juno Therapeutics, Inc v Kite Pharma, Inc.*[1], the United States Court of Appeals for the Federal Circuit reversed a US$1.1 billion judgement against Gilead's Kite Pharma for infringing Bristol-Myers Squibb's Juno Therapeutics cancer immunotherapy patent. Juno's patent at issue, U.S. Patent No. 7,446,190 ('190 patent), relates to a nucleic acid polymer encoding a three-part chimeric antigen receptor (CAR) for a T cell. The decision leaves Bristol-Myers Squibb with far narrower protection, insufficient to prevent competition from its chief CAR T rival, Gilead, and others waiting in the wings.

Overview of CAR T cell therapy

Immunotherapy, a specific type of therapy that uses the patient's own immune system and response to attack tumours, has emerged as a new way to treat cancer. One of the rapidly emerging immunotherapy approaches to treating cancer is adaptive cell transfer (ACT), the most advanced of which is chimeric antigen receptor (CAR) T cell therapy.

The backbone of CAR T cell therapy is the T cells, which are white blood cells that contribute to the body's immune response. T cells play a critical role in both coordinating the immune response and in killing cells that are infected by pathogens. In CAR T cell therapy, the patient's own T cells are isolated and separated from other blood cells. The isolated T cells are then reprogrammed, using a disarmed virus, to produce a specific targeted receptor (a CAR) on each T cell's surface. Importantly, the specific receptor on the CAR T cell allows the T cell to recognize specific antigens on tumour cells. After the T cells are reprogrammed, these CAR T cells are then inserted back into the patient. This is why CAR T cell therapy is sometimes described as a "precision medicine" treatment – it is a treatment tailored to the individual.

Once the CAR T cells are reintroduced into the patient, they multiply and go on to recognize and kill cancer cells that harbour the specific antigen on their surfaces that the CAR T cells have been programed to recognize. Since the CAR T cells continue to multiply after being reintroduced back into the patient, CAR T cell therapy is also sometimes referred to as a "living drug".

The hype surrounding CAR T cell therapy

In recent years, CAR T cell therapy has gained attention due to very promising results in clinical trials, particularly in acute lymphoblastic leukemia (ALL), a blood and bone marrow cancer most common in children. For those patients whose cancer returns after chemotherapy or a stem cell transplant, historically there have been few treatment options available.

CAR T cell therapy has given reason for optimism. In one clinical trial, 79 child patients with ALL received CAR T cell therapy. 82 percent of these patients were in remission within three months after the infusion, and by 18 months post-infusion the overall survival rate was 70 percent.[2] In a second study, 40 percent of adults with diffuse, large B-cell lymphoma showed a "complete response" a year after CAR T cell treatment.[3] CAR T cell therapy therefore gives new hope to patients who were previously unresponsive to conventional therapies or had recurring cancer.

The pharmaceutical industry is currently attempting to harness CAR T therapies for numerous cancers beyond ALL, with a steady increase in CAR T-related patents over the last several years.

Appellate Court limits CAR T patent scope

The first two entrants in the CAR T marketplace were Kite Pharma (now part of Gilead) and Novartis. Juno Therapeutics (now part of Bristol-Myers Squibb) then received approval for its CART T product in early 2021.

Juno had obtained a composition of matter patent, the '190 patent, related to a nucleic acid polymer that encoded a three-part CAR for the T cell.[4] The third portion – the binding element – is the portion of the CAR that determines what target molecule or antigen the CAR recognizes and binds.

One type of binding element in the '190 patent is the single chain antibody variable fragment (scFv). Each variable region has a unique amino acid sequence that dictates how an antibody, and therefore how an scFv, will bind to a target. Specifically, the '190 patent disclosed two scFvs: one derived from the SJ25C1 antibody that binds to the CD19 protein, and a second derived from the J591 antibody that binds to the PSMA protein. Importantly, the '190 patent *did not* disclose the amino acid sequence for either scFv.

Juno sued Kite, alleging that Kite was infringing the '190 patent through the use, sale, offer for sale or importation of Kite's YESCARTA®. There were four claims in issue in this case. Claims 3 and 9, which depended on claim 1, limited the claimed "binding element" from claim 1 to "a single chain antibody", i.e., a scFv. Claims 5 and 11, which depended on claims 3 and 9, further specified that the claimed scFv bound to CD19.[5] Juno alleged that Kite infringed these claims and obtained a judgment for $1.1 billion at trial.

The United States Court of Appeals reversed the trial judgment on the basis that no reasonable jury could find the '190 patent's written description sufficiently demonstrates that the inventors possessed the full scope of the claimed invention.

According to U.S. patent law, the specification must contain a written description of the invention, and the hallmark of the written description is the disclosure.[6] More specifically, when the patent involves genus claims that use functional language, such as the binding function of scFvs claimed in this case, the written description "must demonstrate that the

applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus".[7]

Kite argued that the asserted claims were invalid because they failed to satisfy the written description requirements in that the '190 patent disclosed neither representative species nor common structural features of the claimed scFv genus to identify which scFvs would function as claimed.

The Court of Appeals agreed. The Court found that claims 3 and 9 broadly cover *any* scFV for binding any target. The issue, however, was that the '190 patent's written description failed to provide a representative sample of species within, or defining characteristics for, that expansive genus.[8] The '190 patent contained no details about the two example scFvs species beyond the alphanumeric designations J591 and SJ25C1 for a skilled person to determine how or whether they are representative of the entire claimed genus. In the Court's view, to satisfy the written description requirement, the patent needed to demonstrate to a skilled person that the inventors possessed and disclosed in their filing the particular species of scFvs that would bind to a representative number of targets.[9] The Court of Appeals further found that, in addition to failing to disclose the structural features common to scFvs capable of binding specific targets, the '190 patent also failed to disclose a way to distinguish those scFvs capable of binding from scFvs incapable of binding those targets. Essentially, the '190 patent claimed a problem and all solutions to it, including any compound that is later actually invented and that falls within the claims of the '190 patent. This fails to satisfy the written description requirement.[10]

Claims 5 and 11 were also found to be invalid on appeal. Claims 5 and 11 were limited to scFvs that bind to CD19, a specific target. The Court of Appeals found that the '190 patent provided no details about any CD19 specific scFvs, and instead only provided an alphanumeric designation, SJ25C1, as the source for the CD19-specific scFv.[11] The Court noted that while scFvs in general were known and bind, the record demonstrated that the realm of possible CD19-specific scFvs was vast and the number of known CD19-specific scFvs was small (five at most). The '190 patent, however, provided no details about which scFvs bind to CD19 in a way that distinguishes them from scFvs that do not bind to CD19. As such, without more, the '190 patent could not satisfy the written description requirement.[12]

Insufficient specification and written description in Canada

The United States Court of Appeals reversed the trial judgment because the specification at issue was not sufficient. In Canada, there are similar doctrines relating to the sufficiency of the specification of a patent. The Canadian *Patent Act* [13] requires that a specification be filed[14], and the term "specification" includes both the description and claims of the patent[15]. The requirements for the specification are outlined in sections 27(3) and 27(4) of the *Patent Act*. Under section 27(3) of the *Patent Act*, the specification of an invention must, among other things, correctly and fully describe the invention and its operation or use as contemplated by the inventor.[16] The specification must set out clearly the methods of use in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to use it.[17]

In a similar fashion to the U.S., the disclosure requirement under the *Patent Act* has been described as lying at the heart of the patent system.[18] As such, two things must be described in the description of a specification: the invention, and the operation or use of the invention as contemplated by the inventor. If either element is not correctly or fully described or defined, the patent will be invalid for insufficiency.

If a Canadian court were to follow in the path of the U.S. Court of Appeals for the Federal Circuit, then broad CAR T patents that functionally define CAR T elements with insufficient sequence information would contain insufficient specifications, rendering the patents invalid. Even where sufficient information is provided, the Patent Office may restrict claims to the structural forms disclosed and obvious variants rather than permitting broad functional claims to all compositions that achieve a desired result.

The Federal Court addressed an analogous issue in respect of monoclonal antibodies in *Abbvie Corporation v Janssen Inc*, 2014 FC 55. In that case, Justice Hughes considered functionally-oriented claims to antibodies that bind to a receptor called IL-12 and treat psoriasis, where the claims defined a minimum level of stickiness and potency required to achieve the desired treatment.

Justice Hughes evaluated whether the claims were "overly broad" in comparison to what had been invented and disclosed. In light of the stickiness and potency restrictions within the claims, he found that the claims were not overly broad.[19] The Court considered the claim not to be purely functional in nature and clarified that issues of overbreadth must be considered case-by-case, without any simple principle that can be universally applied.[20]

Justice Hughes' decision was set aside due to an interlocutory matter but without addressing this issue, and the matter was never re-heard.[21] In a later case involving pneumococcal vaccine, the Court sidestepped the issue by interpreting a potentially broad claim narrowly to 13 specified serotypes such that it did not constitute an overbroad claim.[22] The guidance from these and other cases is insufficient to confidently predict what scope a Court would permit for CAR T claims designed to erect meaningful barriers to competitor entry.

The future of CAR T cell therapy in Canada

The scope of exclusive rights conferred by a patent is likely to have a significant impact on access to CAR T therapy in Canada. If broad patents are issued, then the first-movers for any therapeutic target for CAR T will maintain significant barriers to entry. If patents are issued more narrowly, then it will be open to innovators, whether within pharmaceutical companies or in the public or hospital sector or otherwise, to innovate around patents to develop differentiated personalized CAR T therapy.

In Canada, CAR T therapy is currently regulated in the same way as pharmaceuticals, and there are currently two commercial CAR T therapies that have been approved for use in Canada: KYMRIAH® (tisagenlecleucel) and YESCARTA® (axicabtagene ciloleucel).[23] To date, there has been no intellectual property litigation related to either of these products. Generic entrants are unlikely to arise (at least anytime soon) due to the personalized nature of these therapies and unavailability of any abbreviated regulatory pathway.

While CAR T has proven to be promising, only three provinces, Ontario, Quebec and Alberta, cover the costs associated with KYMRIAH®, and the cost is only reimbursed for eligible patients that meet funding criteria (which can include out-of-province patients).[24] The importance of this reimbursement cannot be understated, as KYMRIAH® has a Canadian list price of $450,000.[25] Given how impressive CAR T trials have been, this area appears to be one ripe for further investigation and development.

Unlike typical drugs, CAR T therapy is manufactured not through large-scale chemical or biological processing, but by harvesting and processing individual patients' own cells to enable them to better target cancer cells. Public sector hospitals and other institutions, which are closer to the patient than pharmaceutical companies, may be best-positioned to generate and administer personalized CAR T therapy for patients, provided that the patent

landscape is not overly prohibitive.

The availability of public sector CAR T therapy has the potential to lower CAR T cost by an order of magnitude or more, which may be the difference between CAR T therapy being expanded to new cancers and made widely accessible in Canada or not. Clarity on permissible patent scope for CAR T therapy is therefore of great public importance. In the meantime, life sciences organizations seeking to develop CAR T technology should prioritize patent awareness and strategy in light of the ever-evolving jurisprudence in this area.

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[1] No. 20-1758 (Fed. Cir. 2021) [Decision [PDF]].

[2] Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019; 380:45-56.

[3] The ASCO Post. ASH 2018: ELIANA Trial: Tisagenlecleucel in Pediatric and Young Adult Patients With ALL..

[4] Decision [PDF] at 3.

[5] Decision [PDF] at 4.

[6] Decision [PDF] at 6.

[7] Decision [PDF] at 7.

[8] Decision [PDF] at 9.

[9] Decision [PDF] at 9.

[10] Decision [PDF] at 13.

[11] Decision [PDF] at 16.

[12] Decision [PDF] at 19.

[13] *Patent Act*, RSC 1985, c P-4 [*Patent Act*].

[14] *Patent Act*, s 27(2).

[15] *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Limited,* [1981] 1 SCR 504 at 520.

[16] *Patent Act*, s 27(a).

[17] *Patent Act*, s 27(b).

[18] See for example *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Limited,* [1981] 1 SCR 504 at 517*; Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents),* [1989] 1 SCR 1623 at 1636.

[19] *Abbvie Corporation v Janssen Inc*, 2014 FC 55 at para 168.

[20] *Abbvie Corporation v Janssen Inc.*, 2014 FC 55 at para 178.

[21] *Janssen Inc v Abbvie Corporation*, 2014 FCA 242.

[22] *Merck Sharpe & Dohme Corp v Wyeth LLC*, 2021 FC 317 at para 153.

[23] https://ottawacitizen.com/news/local-news/treating-the-untreatable-how-and-why-canadas-car-t-network-was-built.

[24] https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CAR_T-cellReimbursementPolicy.pdf
https://www.newswire.ca/news-releases/alberta-sites-join-network-of-certified-centres-to-deliver-car-t-therapy-kymriah-r-tisagenlecleucel–837526002.html.

[25] https://nationalpost.com/health/what-price-life-at-a-cost-of-hundreds-of-thousands-a-dose-novel-cancer-killing-drug-sparks-debate.