

TxCeIl

Treg production

Robust and stable Treg manufacturing

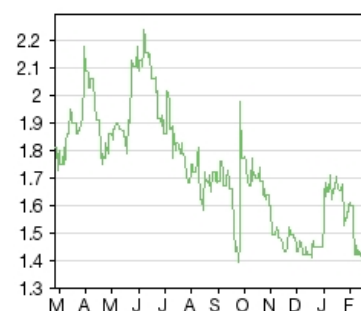
Pharma & biotech

22 February 2018

Price €1.41
Market cap €30m

Cash (€m) at 31 December 2017	4.9
Shares in issue (as of 31 December 2017)	21.8m
Free float	59.45%
Code	TXCL
Primary exchange	Euronext Paris
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(14.8)	(2.9)	(24.3)
Rel (local)	(11.4)	(2.5)	(30.9)
52-week high/low		€2.2	€1.4

Business description

TxCeIl is developing regulatory T-cell therapies against autoimmune and inflammatory disorders. It is now focused on a novel CAR Treg technology platform. A clinical trial in transplantation may file for regulatory authorisation in late 2018.

Next events

2017 results	14 March 2018
Q418	Filing of IND

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**TxCeIl is a research client of
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TxCeIl has disclosed that it has a viable manufacturing route for its novel CAR Treg products. This uses a stable but low-frequency Treg cell type. The TxCeIl methodology uses a robust design to give low inter-patient variability with potentially consistent therapeutic results. Regulatory filings for a dose-ranging clinical trial are expected by late 2018. On the financial side, TxCeIl will need to draw at least €10m of a new, less onerous set of convertible loans to support CAR Treg development. The indicative valuation has been increased to €87.9m from €84.4m as probabilities have been slightly adjusted. Cash on 31 December 2017 was €4.9m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/15	0.92	(10.78)	(88)	0.0	N/A	N/A
12/16	0.15	(12.73)	(98)	0.0	N/A	N/A
12/17e	0.26	(9.48)	(47)	0.0	N/A	N/A
12/18e	0.25	(11.47)	(53)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments. Share issues in 2016 and 2017 reduce EPS.

Focus on CAR Treg with multiple preclinical projects

TxCeIl is set on being the leading Treg company to treat immune disorders using chimeric antigen receptor (CAR) technology; this is similar to that used in the cancer T-cell area. The design of a humanised CAR Treg plus the announcement of a robust manufacturing process have been key development stages. CAR Treg trials as a proof of concept are planned in solid organ transplant rejection. Other projects are at an earlier-stage of research; these could target broader markets.

Making therapeutic CAR Tregs

To make a Treg therapy, TxCeIl needs to isolate enough rare CD45RA+ Tregs; these comprise fewer than 1% of T-cells, transform them using a lentiviral vector and then culture them to get a viable dose. TxCeIl can now run this process in about three to four weeks, which appears commercially viable and similar to current CAR-T cancer therapies. A key clinical aspect will be to determine the effective CAR Treg dose; cancer CAR T-cell products are not a direct analogy.

Valuation: €88m with deal-ready technology

Cash on 31 December 2017 was €4.9m, reflecting an advance payment of €1.4m of the tax credit for 2017 plus careful cost control, although no balance sheet has been published yet. TxCeIl has up to €13.5m of convertible loans available in 2018 out of a €15m drawdown facility, now on better terms. Now that a manufacturing route for CAR Tregs has been clarified, we have increased the probability of a transplant CAR Treg to 13.5% (formerly 12.5%). This raises the indicative value to €87.9m (formerly €84.4m). We assume at least a €10m drawdown of convertible loans in 2018 plus a granted €1.2m Bpifrance loan. The use of convertible loans will lead to further dilution over 2018. TxCeIl is becoming well placed to enter a CAR Treg partnering agreement, although the timing and size of any deal remains uncertain.

Taking the lead in Treg therapy

TxCell is one of the few companies focusing on regulatory T-cell therapy (Tregs) for autoimmune and inflammatory indications. Tregs have very powerful control functions in the immune system and can control adverse immune responses ([Singer et al \(2014\)](#)). TxCell has a big advantage in Tregs as it is the only company known to us to be using CAR technology to improve the efficacy of Treg therapy by specific targeting. The Treg area is underdeveloped and TxCell offers a rare investment opportunity, targeting transplant and major autoimmune indications. The disclosure of a robust manufacturing method has removed a key uncertainty and opened the way to clinical trials in transplantation as a first indication. The area is gaining increased interest with Novartis in an academic collaboration on a new clinical trial in Graft vs Host Disease. Additional information on Tregs, market sizes and the immune system is contained our [outlook note](#) published in February 2017. TxCell continues to explore licensing opportunities for its technologies and products.

TxCell's current Treg pipeline is:

- prevention of solid organ transplant rejection. Lead indication in preclinical;
- bullous pemphigoid (BP) in research;
- multiple sclerosis (MS) in research; and
- lupus nephritis (LN) in research.

In Q418, TxCell plans to file a regulatory dossier to start a first-in-man study in transplantation to provide clinical proof-of-concept of the use of CAR Tregs. The start of clinical development will be subject to regulatory approval and availability of appropriate funding. This first CAR Treg clinical study will be open label and could give validation of the CAR Treg concept by H120.

CAR Tregs: A new area owned by TxCell

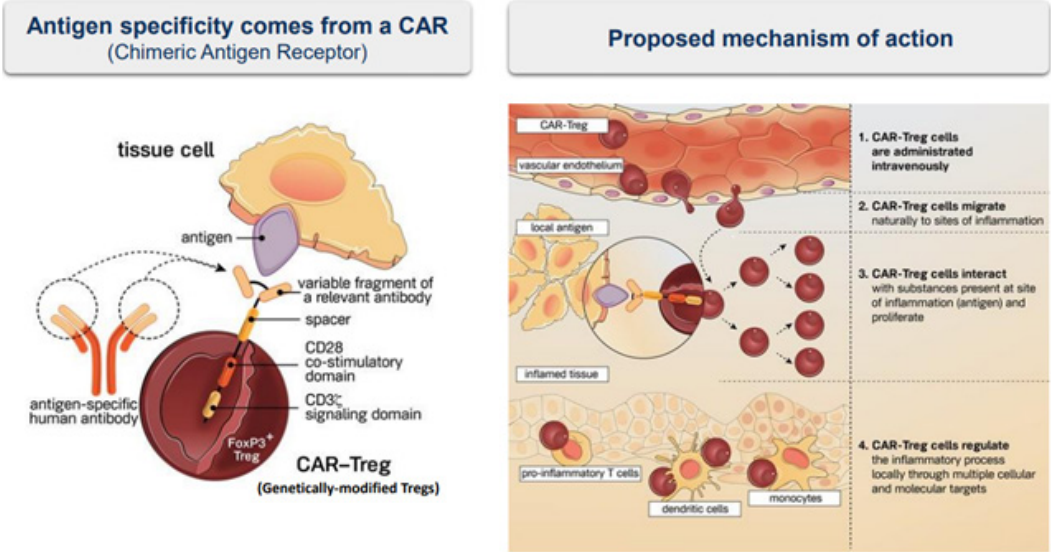
Tregs are used by the immune system to control other immune cells, like CD8+ effector (killer) T-cells, to prevent immune attacks on normal tissues, so generating inflammatory signalling and triggering a widespread immune response. TxCell is developing CAR Tregs that are activated by a specific antigen trigger. Exhibit 1 shows an overview.

CAR Tregs use an antibody fragment as a receptor to target Tregs to specific cell types or locations – like a transplanted organ. The target can be a self-recognition antigen, like HLA (crucial for tissue matching in type, in transplantation), or a natural protein, perhaps as in multiple sclerosis. When a CAR Treg is activated, it limits and deactivates any nearby activated immune cells.

TxCell's CAR Treg platform therefore offers flexible, powerful and precise targeting to any antigen. As the antibody targeting domain of the CAR Treg is humanised, repeat doses of humanised Tregs can be given if needed. The basics of CAR design, a fast-evolving field in the cancer space, are reviewed in our report on [T-cell cancer therapies](#).

The concept of CAR Tregs was published in a patent in 2008 by the Weizmann Institute of Science, Israel, [EP2126054](#). This patent has been granted by the European Patent Agency and was licensed by TxCell in June 2016. It is in the process of examination by the US Patent Office. This patent, where granted, gives broad coverage. To provide further layers of extended protection, TxCell is developing other CAR Treg intellectual property, in the molecular technologies used and in manufacturing and processing technologies.

Exhibit 1: CAR Treg technology and mode of action

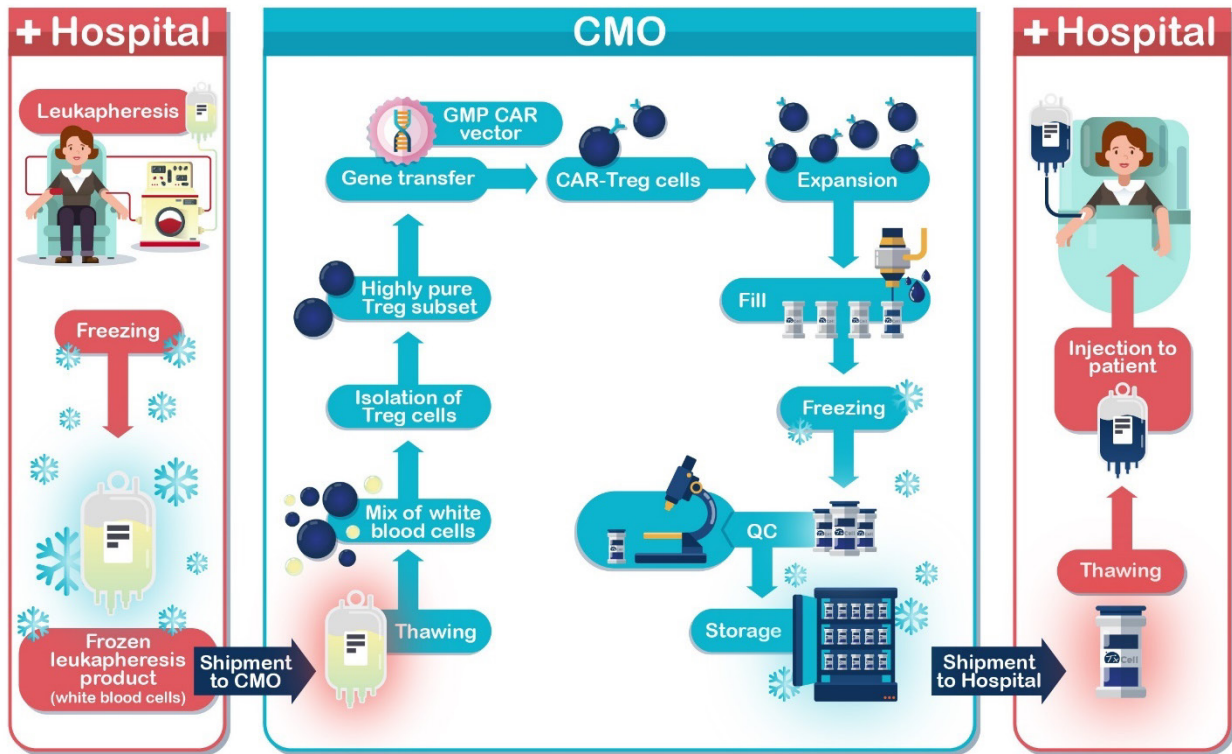


Source: TxCell 22 September 2017 corporate presentation

Manufacturing progress

The process used by TxCell is shown in Exhibit 2. The process involves harvesting patient cells, sending to a manufacturing facility, transfecting with virus and, after culture and testing, returning to the patient for infusion. This process is accepted by regulatory authorities.

Exhibit 2: TxCell's Treg manufacturing process



Source: TxCell

As has been seen with the cancer CD8+ T-cell therapies from Novartis and Gilead (formerly from Kite), manufacturing is a critical part of a CAR T-cell therapy design and delivery. Individual (autologous) cancer CAR therapies are now manufactured and delivered in around 20-25 days. This timing will probably reduce as experience increases and as processes are automated.

TxCell has an agreement with Lentigen Technology for Good Manufacturing Practice (GMP)¹ supply of the lentivirus vector used. The availability of a reliable source of lentivirus is crucial since viral vector manufacturing itself is complex and still laborious. The therapeutic CAR Treg product will then be produced by a contract manufacturing organisation (CMO) to GMP standards for clinical development. Once a contract is agreed, the TxCell-designed process will be transferred to the CMO starting in Q118; it will need to be in place to gain approval for the first clinical trial.

For its first CAR Treg manufacturing process, TxCell has isolated a subset of Treg cells that have been shown to be stable and to display strong anti-inflammatory activity. TxCell will present additional details on this manufacturing process at the CAR-TCR Summit Europe to be held on 20-22 February 2018, in London, UK.

Technical aspects

TxCell has released few details of its manufacturing process as the know-how tends to be commercially confidential. However, TxCell has given Edison more detail on the press release of December 2017 to provide background insight. This is important for the investment case as being able to produce potentially therapeutic doses in a realistic time frame, and (we assume) for a reasonable cost, is a crucial step in the move to clinical development and eventual commercialisation. It is also an aspect that any potential partners will be concerned to see resolved.

The aspects focused on by TxCell to obtain a commercially viable manufacturing system are:

- stability of the Treg cell characteristics (there are different types of T-cell, some of which can inter-convert but the FOXP3 intracellular marker of suppressive Tregs remains constant);
- persistence – once administered to a patient, the CAR Tregs ideally should persist for two to three years at least;
- robust process producing a high-purity selected CD45RA+ CAR Treg subset (see below) – the manufacturing system needs to be reliable and not dependent on high levels of operator skill with no highly variable steps;
- low inter-patient variability – as the starting material is patient dependent, some variability is inevitable but, ideally, the process is capable of delivering a consistent dose of product; and
- the CAR Tregs can be frozen for shipment and thawed for administration with no change in phenotype and function.

There are various types of Treg cells, which are distinguished by different sets of proteins on the cell surface and the presence of the FOXP3 transcription factor – this is an internal cell protein, which activates a specific set of Treg genes. The Treg type used by TxCell is characterised by high levels of cell surface markers CD4, CD25 and CD45RA with low levels of CD127, discussed below.²

Of these, CD4 is a general marker of a wide range of helper and regulatory T-cells separating them from CD8⁺ T-cells, which are the killer T-cells used in CAR T-cell cancer therapy. CD4 is a co-receptor that helps to trigger the T-cell Receptor on the Treg cell if a self-antigen is recognised.

¹ This is the manufacturing standard for clinical use.

² If these are present, there is a + sign added. If low or not present, the sign added is lo/-.

CD25 is a general marker of Treg cells: generally, the more CD25, the better the immune suppressing activity. CD25 is part of the interleukin-2 receptor; interleukin-2 is a key cytokine (immune signalling) molecule that stimulates Tregs and encourages their growth.

TxCell has selected a much more restricted subset of these Tregs that also express CD45RA. CD45, a protein tyrosine phosphatase,³ is a common receptor on many immune cells. The molecular biology of the protein is very complicated and there are multiple types,⁴ which are only seen on specific types of immune cell. In this case, CD45RA is a subtype seen in naïve Treg cells, that is Tregs not yet program themed to respond to a specific self-antigen.

[Seddiki et al \(2007\)](#) looked at the persistence of CD45RA+ Tregs with age. They found that CD25+ Tregs comprise about 10% of the CD4+ population. The number of CD45RA+ cells was about 1% of CD4+ cells. It was also noted this proportion declines with age from age 20 to age 60. TxCell has found about 1% or fewer of CD45RA+ Tregs in its development samples (direct communication).

Naïve Treg cells are produced in the thymus gland and are not common in the peripheral circulation, so hard to harvest. They have the advantage that they are stable in cell culture and can be converted using lentivirus into CAR Tregs that recognise a specific antigen stimulus. In TxCell's first product, this will be an HLA-A2 antigen. If a CD45+ Treg becomes specific for an antigen, it switches from CD45RA to another CD45 subtype: CD45RO. Because it is then programmed to recognise a specific stimulus, this cell type grows rapidly. There are twice as many CD45RO+ cells as CD45RA+ cells in peripheral tissues.

[Canavan et al \(2014\)](#) developed an academic, pilot protocol for growing CD45RA+ Tregs. They noted that "Tregs can be expanded from the blood of patients with CD to potential target dose within 22–24 days". Note that this is longer than the optimised new TxCell process. [Canavan et al \(2014\)](#) used culture conditions of high-dose IL-2, rapamycin and anti-CD3/anti-CD28 beads. The median expansion obtained was about 177x. This was a much higher expansion than obtained for CD45RA- Tregs. It was also noted that the CD45RA+ cells were genetically stable and in particular that the regulatory genes activated by the FOXP3 transcription factor remained activated.⁵ This has also been seen by TxCell. For safety, it is known that some types of CD4+ T-cells can switch and become inflammatory (the Th17 form produces damaging IL-17), but this does not happen with stable CD45RA+ Tregs.

Dose needed – still experimental

CD25+/CD45+ Tregs have excellent inhibitory action and can home to the sites of inflammation ([Canavan et al \(2014\)](#)). The best ratio of Tregs to effector CD8+ T-cells (Teffector) for inhibition seems to be between 1:1 and 1:4. Canavan et al noted about 95% inhibition at a 1:1 ratio, Sedikki noted about 90%. It does seem, therefore, that a low ratio of Tregs:Teffectors at the site of action is best. However, dose and safety will need to be investigated in future clinical trials.

As an exercise in developing a human dose level, rather than for a mouse model, [Gołab et al \(2016\)](#) took white blood cells isolated by leukapheresis. The number of Treg cells in donated blood is too low to be viable but, by circulating the blood through a leukapheresis machine, many more

³ Cells use phosphate groups to activate (usually) or deactivate proteins. In this case when CD45 is activated, it acts inside the cell to remove a deactivating phosphate group from Lck, a tyrosine kinase (lymphocyte-specific protein tyrosine kinase) to activate it. Lck is needed to transmit the signal created when the T-cell receptor binds to its target by adding activating phosphate groups.

⁴ These are splice variants. *CD45* is a large, complicated gene whose message (mRNA) can be configured in multiple ways to give different protein variants with differing functionality.

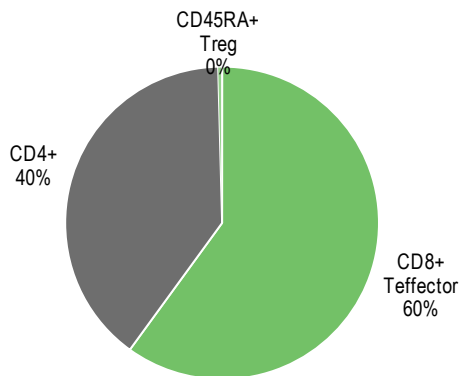
⁵ Cells deactivate genes by adding methyl groups to the DNA backbone. This can be analysed and, as with [Canavan et al \(2014\)](#), the genes activated by the forkhead box transcription factor FOXP3 remain unmethylated and so active.

white immune cells can be isolated. Leukapheresis is also used in the TxCell process; it is a standard procedure.

[Golab et al \(2016\)](#) isolated three billion white cells, of which 1.6 billion were CD4+. The others were CD8+. ⁶ The proportion of CD8 to CD4 T-cells varies widely between patients but it will be approximately 60:40 in many cases. This gave 1.6 billion CD4+ cells. The proportion of Treg cells can vary widely between patients. As CD45RA+ Tregs are 1% or fewer of CD4+ cells, as determined by TxCell, the number obtained might be about 16m (Exhibit 3).

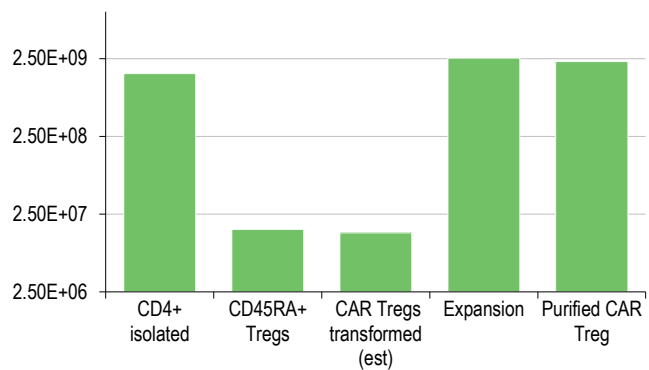
At this stage, TxCell will transform the selected CD45RA+ Treg cells with lentivirus to make CAR Tregs. This is a crucial step for both the efficacy of the CAR Treg cells and for the yield of the process. For illustrative purposes only, we have assumed a transfection efficiency of 90% giving 13m CAR Tregs. Using the 177x expansion seen by Canavan et al would give 2.5 billion cells. With some losses due to quality assurance testing and purification, this might be a human dose of about 2.3 billion CD45RA+ Tregs. Exhibit 4 shows this (log scale). Note that these numbers are purely illustrative as TxCell has not disclosed yields. This shows, on the basis of published work, that a dose in the range used for cancer CAR T-cell therapy could be obtained in under a month.

Exhibit 3: Proportions of CD8+, CD4+ and CD4+/CD45RA+ cells harvested from blood



Source: Edison Investment Research based on [Golab et al \(2016\)](#)

Exhibit 4: Possible yields during production of CAR Tregs



Source: Edison Investment Research based on [Golab et al \(2016\)](#)

Possible dose levels

As yet, we do not have any clinical information about the number of Treg cells required for efficacy in particular indications. [Canavan et al \(2014\)](#) noted a 1:1 to 1:4 ratio as optimal in a controlled in vitro experiment. [Golab et al \(2016\)](#) found a 60% inhibition level in vitro at 1:1 ratios, but this was not a specific CD45RA+ preparation. Neither of these was a CAR Treg. In a mouse model of transplantation, [Lee et al \(2014\)](#) found that giving prior chemotherapy to reduce the number of host effector T-cells was essential for Treg efficacy to control transplant rejection. The dose was high: 5 million antigen responsive Treg cells given to a mouse equals 20 billion directly scaled for a human.

In CAR T-cell cancer therapies, prior chemotherapy conditioning is essential to reduce the number of patient immune cells and allow room for rapid growth of the therapeutic CAR T-cells. TxCell notes that it expects the CAR Treg cells to grow after administration as they are stimulated by the CAR antigen, although the extent is not known and will need clinical determination.

The few published academic clinical Treg studies used polyclonal Tregs - so most would be incapable of controlling a specific immune disease process. In T1D, a 2014 report ([Marek-Trzonkowska et al \(2014\)](#)) in 12 Type 1 diabetic children showed improved levels of endogenous

⁶ There is also a subset of CD8 Treg cells. TxCell and the Center for Research in Transplantation and Immunology, a centre of excellence in the field of transplantation and immunology affiliated to both Inserm and to the Nantes University, have a collaborative research project.

insulin production, with two children ceasing to need insulin injections. The dose was 30m Tregs/kg indicating a dose for an adult 75kg person of 2.3 billion cells; an antigen-specific CAR Treg dose could be much lower as it would be potentially more powerful.

[Bluestone *et al* \(2015\)](#), also in a Type 1 diabetes dose-ranging, 14-patient trial, gave polyclonal Tregs at doses of 5 million (lowest safety dose tested) to 2.6 billion. It is likely that the first TxCell clinical CAR Treg study will follow a similar cautious approach to dosing one patient at a time with at least three-week observations between patients. This leads to a prolonged safety trial period. Interestingly, Bluestone *et al* found that the administered Treg cells were highly persistent and survived for over a year. Finally, [Chandran *et al* \(2017\)](#) used 320 million polyclonal Tregs as a single dose in a small kidney transplant safety study. No efficacy data are available.

Summary of production

TxCell has been able to develop a robust process that appears capable of producing therapeutic doses, as currently understood, of CAR Tregs. This is despite the rarity of the starting cell type. Using a specific type of CD45RA+ allows a stable and robust process. The production time is in line with current CD8+ CAR T-cell cancer therapies despite much less starting material. This advance de-risks a crucial part of the project, opens the way to a validated GMP manufacturing process and so to the first clinical trial. A [video](#) describing the process is available on the TxCell website.

Transplantation indication

TxCell sees the solid organ transplant indication as a good starting indication for its CAR Treg programme. Unless a transplanted organ or tissue is a close match for the HLA type of the host, there is always a risk of rejection where the host immune system attacks the transplant. Mismatch means the number of HLA types that are the same between the donor and recipient. As the HLA system is very polymorphic with six genes to match, it is hard to get exact matches.

The concept is that if a CAR Treg targets and binds to a non-self HLA in the graft, it will be activated locally and suppress direct cytotoxic T-cell and indirect helper T-cell antibody-led responses against the transplanted organ.

The evidence that CAR Tregs can control rejection comes from a paper by Professor Levings of the [University of British Columbia](#) with preclinical work on a mouse antibody fragment CAR Treg targeting HLA-A2 published ([MacDonald 2016](#)). TxCell has a collaboration with this group to target solid organ transplantation. The September 2017 preclinical data on humanised CAR Tregs are not yet published. The project is based on the HLA-A2 CAR Treg discussed above. This will work in about 25% of cases.⁷ TxCell may therefore need to develop other HLA-type CAR Treg constructs.

Possible transplant markets

The market value for Tregs in transplant management is hard to assess. This is a niche opportunity but potentially of high value as long-term management of grafts is not optimal and as these are very expensive procedures. Graft failure is expensive to manage and is often fatal so there are good reasons to use effective Treg therapies. The lung procedure should easily transfer into kidney transplant if efficacy is seen. Tregs may be useful for other organs, like liver, as well but we have not assessed these markets.⁸

⁷ This is because half the population is HLA-A2 positive anyway, so administered Tregs will not specifically target the graft. Of the half that does not carry HLA-A2, half will get a HLA-A2 negative graft on average. This leaves 25% who are HLA-A2 negative hosts with an HLA-A2 positive graft.

⁸ There are about 6,000 liver transplants a year in the US.

In the US in 2016, there were 2,327 lung transplants (see [data](#)). Over 80% of lung transplants had four or more HLA mismatches so have higher rejection risk. Survival of lung transplant patients is not good at about 50% after five years. A [2014 report](#) indicates 1,809 lung transplants in Europe. Initial lung transplant data are planned to be available in 2020 or 2021. This may be enough for a named patient approval but a larger study will probably be needed, especially for an FDA approval, so 2024 is used tentatively as the expected date.

In the US in 2016, there were 13,431 deceased donor kidney transplants ([OTPN data](#)). About 75% of deceased kidney donor grafts had four or more mismatches so are at higher risk of rejection. Kidney grafts are better managed but as a larger market offer more commercial upside. There is a high medical need if a graft starts to fail due to rejection. The European markets are more fragmented. A [2014 report](#) showed 9,912 deceased donor transplants.

An initial value assessment is shown in Exhibit 5. This is tentative but reflects known parameters. It is based on lung and kidney grafts. The patient column is the number of transplants (lung) or deceased donor grafts (kidney) each year.⁹ Accessible patients are 25% of this due to HLA type. A further adjustment is made based on the level of four or more mismatches. We estimate a relatively high market share based on medical need, although lower in the EU due to funding limits. The price used is US\$475,000 in line with Kymriah, the CAR T-cell therapy from Novartis. NPV are calculated from 2024 for 12 years' biological exclusivity in the US and 10 in the EU based on an assumed 25% post-tax net margin. An alternative scenario would be a partnering deal. If so, earlier upfront payments with a lower cash flow based on royalties would be assumed instead. It seems possible that TxCell, with funding, could develop the small and specialist centre-based transplant niche.

We have increased the probability for lung to 13.5% from 12.5% to reflect the manufacturing process, which reduces risk. This is high for preclinical, but cell therapies have been approved by the FDA on fast track with limited data compared to mainstream drugs. As kidney is less well defined, it is now given an 8.1% probability, updated in line with lung from 7.5%.

Exhibit 5: potential transplant market for CAR Tregs

	Patients	Accessible	Share	Treated	Peak value (€m)	NPV	Probability	Indicative value (€m)
Lung transplant								
US	2,327	465	80%	372	€150	€93.2	13.5%	12.6
EU	1,809	362	60%	217	€88	€51.9	13.5%	7.0
Kidney transplant								0.6
US	13,431	2,518	50%	1,259	€508	€315	8.1%	25.6
EU	9,912	1,982	30%	595	€240	€142	8.1%	11.5
								37.1
Total	27,479	5,327	46%	2,443	986	603		56.7

Source: Edison Investment Research

Adding in other HLA types will extend use rates and add value but as these are separate development projects, they are not included in our current forecasts.

Funding and equity

The February 2017 funding raised €11.01m gross and issued 5,549,300 shares plus tradable warrants. However, given the current share price, the warrants will not be exercised.

Of the 2016 Yorkville Advisors Global (YAG) funding using convertible loan tranches, all the loans have converted resulting in the issue of 3.14m new shares for €4.9m cash. The last three tranches

⁹ Kidney donors can be living – usually a relation who donates one kidney – or deceased, such as a road traffic accident victim who was brain damaged but otherwise intact and healthy. The latter is a more variable source of transplant material. Lung and other organs donors are all deceased.

were converted on 27 December 2017. The 686,350 warrants issued (0.35m at €4.29 and 0.34m at €2.97), will give a further €2.5m cash if exercised.

In November 2017, TxCell agreed revised terms on a further €15m of convertible loans. The terms are more favourable to TxCell than originally agreed in 2016. These new convertible loans can be drawn monthly as needed from February starting with a €1.8m tranche and then monthly tranches of €1.175m. This potentially gives a €13.5m drawdown for 2018. Exhibit 6 has updated details. Note that TxCell only plans to use this drawdown facility until sustainable funding can be put in place.

We do not expect a full drawdown of these loans and as they will be staged as required, the commissions and warrants depend on the future share price. For illustrative purposes, at a share price of €1.39 (Feb 17 2018), €10m of the new convertible loans might lead to a gain of €9.8m in cash, with the issuing of 0.4m shares in commission fees and 7.6m shares after loan conversion, although this obviously depends on the share price at the time of conversion. There could also be a further 0.83m warrants at €3 (minimum value) yielding €2.5m cash if and when exercised. That would leave a further €5m of convertible loans available to fund TxCell into 2019. However, costs on projects and for preparing for the transplant clinical trial may be higher than we expect.

Exhibit 6: Tranche loan note revision details

Aspect	Revised 2018 terms	Former terms
Amounts	€15m available issued at TxCell's request in monthly tranches. In 2018, drawdown starts with a €1.8m tranche and then monthly tranches of €1.175m making up to €13.5m.	€5m drawn in 2016 plus €15m available from 2018
Discount to cash	The cash value of each note is 98% of the nominal value.	98% of the nominal value.
Interest	There is no interest payment on the loan amount	Same
Commitment fee	This is 2% of the loan value (€300k) paid in cash. In 2017, €100k was paid.	This is 5% of the loan tranche value paid in shares.
Conversion base price	This will be at a 5% discount to the volume weighted average share price for the previous 10 days. YAG can convert individual tranches of €0.1m as it wishes.	Discount was 7% for the 2016 loans.
Conversion period	Loans are normally converted to shares and sold quickly. If the loans are not converted, they are repaid after 14 months at face value.	Same
Warrants	For each €100k tranche of convertible loan notes, €25k of warrants will be issued. The warrants will not be listed but they can be traded. There is a five-year exercise period. They provide cash if exercised.	For each €100k tranche of convertible loan notes, €50k of warrants was issued. There are now 686,350 warrants issued from the 2016 €5m loan funding.
Warrant exercise price	Warrants convert at 130% of the volume weighted average share price with a minimum of €3 over the preceding 10 days before the loan note is issued. Warrants have a five-year duration.	Warrants convert at 115% of the volume weighted average share price in the preceding 10 days. These warrants were issued in H216 so expire in H221.

Source: Edison Investment Research based on TxCell announcement

Zero interest Bpifrance loans

TxCell has access to interest-free loans¹⁰ from [Bpifrance](#), a French government agency. The new €1.2m loan covers about half the eligible costs of the expected €5m project on the HLA-A2 CAR Treg cellular therapy for transplant. It will fund the preclinical work and the technology transfer to the CMO of the new production methodology.

Sensitivities: CAR Tregs create major opportunities

The CAR Treg opportunity is developing well with four potential indications disclosed and others in research. New patents have been filed on the transplant indication. A clinical proof-of-concept study in transplant is expected to start, probably in H119 (formerly Q418) if filing of a trial design for approval by regulators in Q418 is on schedule. Results might be possible in 2020. This will be the first CAR Treg study and a milestone in the development of the technology. TxCell has a granted European blocking patent until 2028; this is still under examination in the US, but may need other IP licences. Finally, the sources of 2018 cash are currently limited to excellent but limited Bpifrance

¹⁰ The Bpifrance loan is an interest-free innovation loan entitled Prêt à Taux Zéro pour l'Innovation (PTZI). This financing supports companies to develop innovative products with real commercial potential.

loans and the advance of the tax credit. We also note that the revised convertible loan agreement will be unpredictable in its impact on the share price. Positively, as a technology platform, CAR Treg has a high deal potential especially with a robust manufacturing route now established. However, major deals may be delayed until the first product is at least in clinical development.

Valuation: indicative value adjusted, dilution uncertain

We revised the TxCell valuation in our last note to €84.4m. We have further increased this slightly to €87.9m due to the revised probability on transplant indications discussed above.

Exhibit 7: TxCell adjusted indicative valuation			
Item	Basis/probability	Subcategory (€m)	Total (€m)
CAR Treg transplant, lung	13.5%	19.59	
CAR Treg transplant, kidney	8.1%	37.07	
CAR Treg Multiple sclerosis	Nominal	10.0	
CAR Treg Bullous pemphigoid	Nominal	5.0	
CAR Treg Lupus Nephritis	Nominal	7.5	
Value of indications			79.2
CAR Treg potential partnering	25%		35.5
Ovasave	Nominal		20
Overall value of indications			134.6
R&D (ex-trial costs)		(32.2)	
CAR Treg trials to 2021		(12.5)	
General and administrative		(9.5)	
Costs less tax credits to 2021			(54.2)
Tax credits			13.1
Debt NPV (@1.5%)			(5.6)
Pre-funding and dilution value			87.9

Source: Edison Investment Research (amounts rounded to 1 decimal place)

The indicative value per share based on 21.8m shares in issue as of 31 December 2017 is €4.11 (Exhibit 8). However, this is likely to be diluted by further share issues in 2018. If the convertible loans issued are to a value of €10m, then 8.79m new shares and warrants based on a market share price of €1.39 might be issued. This implies a value of about €2.88 per share before management options. However, there is a lot of uncertainty in these per share numbers as they are affected by share price movements and the extent and timing of convertible loan conversions.

Exhibit 8: Indicative value per share			
	Shares (m)	Cum total (m)	Value/share (€)
Current	21.81	21.81	4.11
Warrants and loan conversions 2018 only	8.76	30.58	2.88
Management options	1.89	32.47	2.71

Source: Edison Investment Research

Financials

The 2017 operating cash outflow, as disclosed in the Q417 report by management, was €9m. There was an advance tax credit payment for 2017 of €1.4m. TxCell has sold its 2016 and 2017 research tax credits to Predirec Innovation 2020, and so receives part of the tax credit within the year with the balance treated as a receivable. These factors enabled TxCell to finish 2017 with €4.9m of cash. However, the cash flow may not include the €2m Trizell payment due in December 2017; if this payment was not made in December, effective cash was €2.9m. Accounts for 2017 will be published on 14 March.

The 2018 cash outflow before funding indicated by our forecast is about €15m (of which €4m is due to Trizell), offset by the €1.2m Bpifrance loan and €10m of convertible loans plus a further advance

tax credit of €1m. A state loan taken to fund Ovasave development is now due for repayment at €0.34m/year. Total operating costs are likely to rise due to manufacturing and preclinical, and regulatory costs. Other projects are also likely to need more funding as one or more could move into preclinical development. Our updated financial estimates are shown in Exhibit 9; TxCell has not provided any guidance.

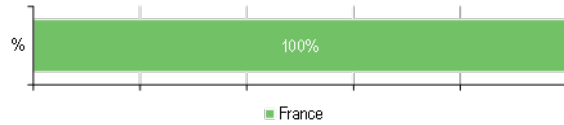
Exhibit 9: Financial summary

	€000s	2015	2016	2017e	2018e
Year End December		IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue		920	153	262	250
Tax refund		3,718	2,794	2,000	2,000
Cost of Sales		0	0	0	0
Gross Profit		4,638	2,947	2,262	2,250
EBITDA		(10,797)	(11,946)	(9,262)	(11,250)
Operating Profit (before amort. and except.)		(9,662)	(12,046)	(9,362)	(11,350)
Intangible Amortisation		0	0	0	0
Exceptionals		(1,167)	(87)	0	0
Share based payments		(483)	(649)	(587)	(587)
Operating Profit		(11,312)	(12,783)	(9,949)	(11,937)
Net Interest		42	(18)	4	2
Profit Before Tax (norm)		(10,782)	(12,733)	(9,480)	(11,470)
Profit Before Tax (FRS 3)		(11,297)	(13,569)	(10,167)	(12,157)
Tax		0	0	0	0
Profit After Tax (norm)		(10,782)	(12,733)	(9,480)	(11,470)
Profit After Tax (FRS 3)		(11,297)	(13,569)	(10,167)	(12,157)
Average Number of Shares Outstanding (m)		12.2	13.1	20.2	21.8
EPS - normalised (c)		(88.4)	(97.5)	(47.0)	(52.6)
EPS - (IFRS) (c)		(92.6)	(103.9)	(50.4)	(55.7)
Dividend per share (c)		0.0	0.0	0.0	0.0
Gross Margin (%)		NA	NA	NA	NA
EBITDA Margin (%)		NA	NA	NA	NA
Operating Margin (before GW and except.) (%)		NA	NA	NA	NA
BALANCE SHEET					
Fixed Assets		6,938	7,032	7,004	6,954
Intangible Assets		5,907	5,911	5,933	5,933
Tangible Assets		876	799	749	699
Other		155	322	322	322
Current Assets		13,782	5,763	7,672	2,943
Stocks		0	0	0	0
Debtors		1,551	1,381	1,384	1,384
Cash		9,208	3,482	4,888	559
Other		3,023	900	1,400	1,000
Current Liabilities		(7,467)	(7,893)	(6,791)	(2,847)
Creditors		(7,467)	(7,724)	(5,914)	(1,970)
Short term borrowings		0	(169)	(877)	(877)
Long Term Liabilities		(1,664)	(3,710)	(2,021)	(12,856)
Long term borrowings		(1,641)	(3,650)	(1,071)	(11,906)
Other long term liabilities		(23)	(60)	(950)	(950)
Net Assets		11,589	1,192	5,864	(5,806)
CASH FLOW					
Operating Cash Flow		(10,108)	(10,417)	(9,028)	(15,066)
Net Interest		42	(18)	4	2
Tax		0	0	0	0
Capex		(214)	(337)	(100)	(100)
Acquisitions/disposals		(5,879)	0	0	0
Equity financing		7,631	270	10,058	0
Other		3,818	4,776	460	10,835
Net Cash Flow		(4,710)	(5,726)	1,394	(4,329)
Opening net debt/(cash)		(12,290)	(7,567)	337	(2,940)
HP finance leases initiated		0	0	0	0
Other		(13)	(2,178)	1,883	(10,835)
Closing net debt/(cash)		(7,567)	337	(2,940)	12,224

Source: Company accounts, Edison Investment Research

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Revenue by geography

Management team
CEO: Stéphane Boissel

Stéphane studied management and finance at the University of Lyon, France, graduated at Paris-Dauphine and obtained his MBA from the University of Chicago (Booth GSB). He has worked for PwC and Lazard. He was CFO at Innate Pharma, then from 2010 to 2014 he was deputy CEO of Transgene. Before joining TxCell, was CEO of Genclis, a molecular diagnostic company.

Chairman of the Board and Head of Research: François Meyer

François graduated from the Swiss Federal Institute of Technology in Zurich. He received his PhD from the Institute for Molecular Biology at the University of Zurich, held various executive R&D positions at Ciba-Geigy Pharma, Sandoz Pharma, Rhone Poulenc Rorer (head of global research) and was head of R&D at Aventis Pharma, France. He is CEO of Centelion, an affiliate company of Aventis Pharma. François joined TxCell as CEO in 2011 and became chairman of the board in 2012 and head of research in 2016.

FD : Raphaël Flipo

Raphaël graduated from business school (EDHEC, Nice) with a specialisation in corporate finance and holds a Master's degree in tax and business law. He worked for PwC and then joined Lionbridge Technologies. He joined TxCell in 2013 as chief financial officer.

Principal shareholders (TxCell to update if possible)

	(%)
BpiFrance	30.8%
Auriga Partners	19.1%

Companies named in this report

Novartis, Gilead

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