Health Policy Advisory Committee on Technology

Technology Brief

Allogeneic mesenchymal stem cell and autologous T-cell therapies for the treatment of refractory Crohn's disease

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Adelaide Health Technology Assessment

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HealthPACT
emerging health technology

HealthPACT Secretariat
c/o Healthcare Improvement Unit, Clinical Excellence Division
Department of Health, Queensland
Level 2, 15 Butterfield St
HERSTON QLD 4029

Postal Address: GPO Box 48, Brisbane QLD 4001

Email: HealthPACT@health.qld.gov.au Telephone: +61 7 3328 9180

Electronic copies can be obtained from: http://www.health.qld.gov.au/healthpact

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This Brief was prepared by Benjamin Ellery and Jacqueline Parsons from Adelaide Health Technology Assessment, University of Adelaide.

Summary of findings

Allogeneic mesenchymal stem cell and T-cell therapies to treat refractory Crohn's disease are still in a developmental phase, with no indication to suggest any influence on clinical practice in Australia and New Zealand. Most evidence on the technologies is limited to case series.

One published randomised controlled trial funded by TiGenix considered the safety and effectiveness of Cx601 therapy (which uses allogeneic mesenchymal stem cells) compared to placebo. The results suggested that Cx601 led to clinical remission in 50 per cent of patients who received the therapy, while 36 per cent of placebo patients had remission of their symptoms, a mean difference of about 15 per cent (p=0.02). Safety outcomes for Cx601 and placebo were comparable, though establishment of treatment-relatedness for adverse events was insufficient. Notably, the study followed patients for 24 weeks and the study authors commented that long term follow-up results are required.

Information from the developer of Ovasave (TxCell) suggests this technology is unlikely to cause an immediate impact to the Australian or New Zealand healthcare systems, as the technology is undergoing a redevelopment phase. New iterations of this technology may be available for consideration by HealthPACT in the future.

HealthPACT Advice

Therapies such as stem cell treatment should be considered investigational and would only be applicable to a small proportion of patients with refractory Crohn's disease who had failed conventional treatments.

HealthPACT does not support public investment in this technology in routine clinical practice and recommends that stem cell treatments should only be used under the auspices of a well conducted clinical trial. HealthPACT recommends that this technology be monitored for further information in 24-months.

Technology, Company and Licensing

Register ID	**WP257**
Technology name	**Allogeneic mesenchymal stem cell and autologous T-cell therapies**
Patient indication	**Refractory Crohn's disease**

Description of the technology

One autologous T-cell therapy, Ovasave® (TxCell, Valbonne, France), was identified for inclusion in this Brief. Ovasave® based on the proprietary Antigen Specific Treg for Inflammation and Autoimmunity (ASTrIA) process uses autologous antigen specific Type 1 Regulatory T cells (Ag-Treg) to treat inflammatory bowel disease (IBD).[1] The TxCell website specifies that this technology currently remains in the 'development pipeline'; a phase IIb clinical trial (CATS29) is underway to investigate the use of this therapy specifically for moderate to severe refractory Crohn's disease. Further description of the product and schematics that explain how the treatment is manufactured and the mechanism of action are also available from the website.[a] In principle, manufacturing involves *ex vivo* 'education' of the patients own purified T cells, which are mass-cultured and stored for multiple doses over a treatment period of several years. When a patient's own Ag-Treg cells are intravenously re-injected, they migrate to target inflammation sites within the bowel. At these inflammation sites, they become activated by a specific antigen. Upon activation, Ag-Treg cells release localised immunosuppressive factors, cell-cell contacts and cytotoxic compounds, which are claimed to treat the inflammation.[1]

Based on a literature search, allogeneic mesenchymal stem cell therapies (aMSCTs) for Crohn's disease have been researched by two study groups; one funded by DigestScience Foundation (Lille, France)[2], and the other group funded by European cell therapy company, TiGenix (Leuven, Belgium and Madrid, Spain), the developer of Cx601.[3]

Cx601 is a suspension of aMSCTs, or specifically, expanded *adipose-derived* stem cells (eASC) which are administered by local injection.[4] Cx601 is an investigational agent under development for the treatment of complex perianal fistulas in Crohn's disease patients that have failed standard therapy including immunosuppressants, antibiotics, or anti-TNF therapies. In 2009, the Cx601 was granted orphan designation by the European Medicines Agency for the treatment of anal fistulas, given the debilitating nature of this condition and that standard treatment options are often ineffective.[4]

The proprietary method for eASC, as decribed by TiGenix is available from the company website,[b] but pictures or diagrams illustrating the technology are not featured. Notably, the

[a] http://www.txcell.com/technology/astria/

[b] http://www.tigenix.com/en/page/18/easc

process described by the company is generic to range of diseases and has applications outside the patient indication for this Brief. In the research setting, a protocol for cell expansion, transport, storage and administration has been described by Panes et al (2016), who conducted a clinical trial using Cx601 for the treatment of anal fistula in Crohn's patients.[3]

Briefly, Panes et al isolated Cx601 cells from the stromal vascular fraction of lipoaspirates from healthy adult donors using liposuction.[3] Cells were expanded according to standardised cell culture practices and kept cryopreserved until required for use. Cells from a single donor were used in each Cx601 dose. Before administration, 120 million cells were formulated in 24 mL of culture medium and shipped in four vials (6 mL) to a hospital site ready for use by a surgeon the same day (the maximum storage life being 48 hours at 15 to 25˚C). Panes et al described an administration procedure that used a fine 20 gauge long needle to inject Cx601 via the anal canal into surrounding fistula tissue, previously sutured.[3]

Company or developer

TxCell and TiGenix are the developers of ASTrIA based on Ag-Treg and Cx601 based on aMSCs for the treatment of Crohn's disease, respectively. Cx601 is indicated for the treatment of refractory perianal fistula in Crohn's disease.

Reason for assessment

Although treatment with aMSCTs and autologous T-cell therapies for Crohn's disease may be applicable to a small proportion of the Australian/New Zealand population, they may have far-reaching benefits. However, these types of therapy may pose patient safety concerns.HealthPACT suggests that aMSCTs and autologous T-cell therapies for Crohn's disease are applicable to a small proportion of the Australian/New Zealand population but may have far-reaching benefits. However, HealthPACT also considers that these types of therapy may pose safety concerns.[c]

Stage of development in Australia

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational (BA alone)
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

[c] Based on the Error! Reference source not found. discussion, we did not identify literature which confirmed these particular concerns. Other stem cell therapies which employ the use of allogeneic cells of *haematopoietic* origin have been noted to have important safety issues relating to toxicity, based on results of a recent RCT published in the *The Journal of the American Medical Association*, which may be grounds to preclude their recommendation in the management of refractory Crohn's disease. See Error! Reference source not found. for details.

Licensing, reimbursement and other approval

The two cellular therapies offered by TxCell and TiGenix were noted by both companies as being in the development pipeline. Therefore, the therapies are considered to be pre-commercial and no information on licensing or approval is yet applicable. Each company was contacted for further comment, but neither responded with the requested information.[d] See Error! Reference source not found. for details.

Australian Therapeutic Goods Administration approval

☐ Yes ARTG number (s)

☒ No

☐ Not applicable

Technology type	**Procedure**
Technology use	**Therapeutic**

Patient Indication and Setting

Disease description and associated mortality and morbidity

Crohn's disease is a chronic illness of unknown aetiology but is immunologically mediated.[5] It is characterised by inflammation of the intestinal mucosa and follows a relapsing-remitting course, without known cure. Standard therapeutic options include lifestyle modifications such as diet and exercise, anti-inflammatory drugs, immunosuppressants and biologics such as anti-tumour necrosis factor (TNF)-α antibodies. Surgery may be indicated where medical management does not provide adequate relief, however, surgery involves removing the diseased part of the intestine and is not definitive. Surgery is associated with complications such as short gut syndrome and recurrence may be a problem even after surgery. As many as ten per cent of patients remain seriously ill after all therapeutic options have been exhausted and may have ongoing nausea, abdominal pain, vomiting, diarrhoea, malnutrition, non-intestinal symptoms such as skin lesions, eye inflammation and arthritis, and psychological distress. Fistula formation is also a common complication, and growth retardation may occur among children. For patients with refractory Crohn's disease, treatment cannot prevent the need for intensive surgery to repair complications including obstructions, fistulae and abscesses. Multiple surgeries can lead to short-gut syndrome, chronic parenteral nutrition, and liver failure.[5]

Crohn's and Colitis Australia (CCA) have noted that Crohn's disease is predominantly a disease of the developed world.[5] The prevalence of Crohn's disease has noticeably increased in recent decades and the condition's severity has worsened. Onset is most common in

[d] Email correspondence sent 12 April 2017.

young adults (onset peaking between 15 and 40 years). The estimated incidence of Crohn's disease in Australia is high even when compared with other countries that have high rates of Crohn's disease.[5]

HealthPACT previously considered novel treatments for refractory Crohn's disease in 2014. Since that time, no more recent epidemiological estimates of the Australian and New Zealand disease burden due to Crohn's disease were identified in the literature or relevant databases held by the Australian Institute of Health and Welfare and New Zealand Ministry of Health. The 2014 HealthPACT Brief found that:

> "An estimated 75,000 Australians have inflammatory bowel disease (Crohn's disease or ulcerative colitis), with a significant increase expected over the next decade. The numbers were not presented separately for Crohn's disease versus ulcerative colitis in the CCA report, but other Australian documents report that 46 to 60 per cent of cases of IBD are Crohn's colitis. In the first prospective, Australian population-based IBD incidence study (data collected in Victoria from 2007 to 2008), the age-standardised IBD incidence rate was estimated at 30 per 100,000, with an estimated prevalence of 68,000 to 74,000 (or one person, aged from 5 to 49 years, in 250). Another published prevalence estimate specific to Crohn's disease was 28,000 Australians affected, with 800 people newly diagnosed annually, most of whom are young adults. Incidence and prevalence estimates for New Zealand could not be found."[5]

Speciality	**Immunology and allergy**
Technology setting	**Specialist hospital**

Impact

Alternative and/or complementary technology

Only limited information was available in the preparation of this Brief, and we had no direct comment from the applicable companies. Noting these limitations, the two most relevant categories for the technology are considered to be:

- additive or complementary technology, i.e. the new technology is used alongside the current technologies, in combination with but not replacing them
- additive and substitution, i.e. the new technology can be used as a substitute in some cases, but may be used in combination with current technologies in other instances.

Current technology

There is no existing cure for Crohn's disease. As a chronic condition, lifetime care is indicated, usually commencing in early adulthood in otherwise healthy, active people. Treatment goals, as noted in clinical guidance published by the Gastroenterological Society of Australia (GESA) are to:

- "treat acute disease:
    - reduce or control intestinal inflammation and if possible heal the mucosa
    - minimise side-effects and long-term adverse effects
    - eliminate symptoms (abdominal pain, diarrhoea and rectal bleeding)
- improve and maintain the patient's general wellbeing (optimising the quality of life)
- correct nutritional deficiencies
- maintain steroid-free remissions (decreasing the frequency and severity of recurrences and reliance on steroids)
- prevent complications, hospitalisation and surgery."[6]

Treatment to control inflammation and provide the opportunity for the gastrointestinal tract to heal is achieved using five classes of medications: aminosalicylates (5-ASA), corticosteroids, immunomodulators (e.g. azathioprine, 6-mercarptopurine and methotrexate), biological agents (including infliximab and adalimumab), and antibiotics (including metronidazole, ampicillin and ciprofloxin).[6] Generally, the aminosalicylates are a first-line therapy indicated on initial presentation of symptoms, and corticosteroids may be used to treat acute inflammatory flare-ups that are contraindicated or nonresponsive to adequate 5-ASA dosing. Immunomodulators are used to further control inflammation and maintain disease remission as corticosteroids are tapered and discontinued. Biological agents, can be prescribed by a specialist gastroenterologist if the aforementioned treatments fail, but not all patients can tolerate the TNF-α antibodies typically used, and as with the other Crohn's medications, this class of medication is not curative. Antibiotic therapy can be used to induce remission of Crohn's disease, but is contraindicated for maintenance therapy. Antibiotics may be used for treatment of complications including perianal disease, fistulae, inflammatory masses, and bacterial overgrowth in the presence of strictures. When all medical therapy fails, surgery is a last resort, or may be used in some cases of complication including stricture, obstruction, perforation, abscess, and bleeding. Surgery is not curative, as recurrence and complications can still be a problem after multiple operations.[6]

Diffusion of technology in Australia

The relevant technologies are under development in the USA, the UK or continental Europe and no evidence to suggest they are in use in Australia or New Zealand was identified.

International utilisation

Country	Level of Use		
	Trials underway or completed	Limited use	Widely diffused
UK	✓		
Continental Europe	✓		
Israel	✓		
USA	✓		

Cost infrastructure and economic consequences

No information on cost is available and no responses to requests for information from TxCell or TiGenix were forthcoming, therefore we cannot report on economic impacts to the Australian or New Zealand healthcare systems that have not already been considered in the previous HealthPACT Brief published in 2014.[5] For details, this document can be accessed online.[e]

Ethical, cultural, access or religious considerations

No issues were specifically identified from the results of the literature search. However, access to the treatments identified in this Brief will depend upon access to specialist healthcare facilities, likely located in large urban centres. As such, patients in remote and rural locations who are clinically indicated for the treatment will be required to travel in order to benefit, should the technology diffuse to the Australian and New Zealand healthcare systems.

Evidence and Policy

Safety and effectiveness

The literature search found only one small case series of 20 patients (level IV intervention evidence) reporting on the safety and effectiveness of Ovasave®[8]; other than this study, only conference abstracts reporting on Ovasave® were identified. The case series reported that treatment was well-tolerated based on the adverse events profile and that a statistically significant response was observed among 40 per cent of patients, while symptom reduction consistent with remission was observed in three patients.[8] Further evaluation of Ovasave®

[e] https://www.health.qld.gov.au/__data/assets/pdf_file/0037/428599/wp184.pdf

may be warranted once the phase IIb clinical trial (CATS29) investigating the use of this therapy for moderate to severe refractory Crohn's disease is published.

A recent meta-analysis, that included a range of stem cell therapies for Crohn's disease [9]suggested a promising role for stem cell therapy in IBD, inclusive of Crohn's disease and ulcerative colitis, but that substantial challenges such as 'cost and inadequate/incomplete characterization of effect, limit their current use in clinical practice.' The meta-analysis was comprised of only single-arm studies (i.e. *case series*) which were usually described as phase I trials, enrolled fewer than ten patients, and of the seven included studies, three were published by the same author prior to 2010. Given the evidence presented by Dave et al[9] is low level, includes a small patient number, and three of the studies meta-analysed are more than 10 years old, this evidence is not further considered here.

Conversely, recent level II evidence was identified informing the discussion for the safety and effectiveness of aMSCTs for refractory Crohn's; one non-industry RCT[2] and one RCT sponsored by TiGenix, which reported on Cx601.[3]

Table 1 Efficacy of Cx601 versus to placebo for the treatment of fistulising refractory Crohn's disease[3]

Outcome	Cx601 (n=107)	Placebo (n=105)	% mean difference [95%CI]	p-value, group difference
Combined clinical remission by week 24	53 (50)	36 (34)	15.2 [0.2, 30.3]	0.02
Clinical response by week 24	71 (66)	56 (53)	13.0 [-0.1, 26.1]	0.05

Data are number (%), unless otherwise specified

Panes et al (2016)[3] conducted a randomised controlled trial (RCT) including 212 refractory Crohn's disease patients (≥18 years) with draining, complex perianal fistulas allocated to treatment with a single intralesional injection of Cx601 cells or placebo (24 mL saline injection). Treatment was administered by an unmasked surgeon; however, a blinded gastroenterologist and radiologist assessed the therapeutic outcome. The primary outcome was combined clinical remission at 24 weeks, i.e. closure of all treated external openings that were draining at baseline as assessed by clinical examination, and the absence of collections larger than two centimetres of the treated perianal fistulas as per blinded analysis by magnetic resonance imaging (MRI). Clinical response was also assessed, defined as closure of at least 50 per cent of all treated external openings found to be draining at baseline, after 24 weeks follow-up. These outcomes are summarised in Table 1.

Safety outcomes reported up to the 24-week follow-up included "treatment-emergent adverse events (TEAEs), TEAEs related to the study treatment (i.e. Cx601) serious TEAEs, serious TEAEs related to the study treatment, TEAEs leading to study withdrawal, procedure-emergent non-TEAEs, and deaths" (Table 2). Apart from the definitions provided

in Table 2, TEAEs and other adverse events were not further defined.[f] The authors reported that no deaths occurred.

Table 2 Safety data for Cx601 versus to placebo for the treatment of fistulising refractory Crohn's disease[3]

Outcome	Cx601 (n=103)	Placebo (n=102)
TEAEs overall	68 (66)	66 (65)
TEAEs leading to study withdrawal	5 (5)	6 (6)
TEAEs in ≥5% of patients in either treatment group		
Proctalgia	13 (13)	11 (11)
Anal abscess	12 (12)	13 (13)
Nasopharyngitis	10 (10)	5 (5)
Diarrhoea	7 (7)	3 (3)
Abdominal pain	4 (4)	6 (6)
Fistula[a]	3 (3)	6 (6)
Treatment-related adverse events	18 (17)	30 (29)
Treatment-related adverse events in ≥2% of patients in either treatment group		
Anal abscess	6 (6)	9 (9)
Proctalgia	5 (5)	9 (9)
Procedural pain	1 (1)	2 (2)
Fistula discharge[b]	1 (1)	2 (2)
Induration	0	2 (2)
Serious TEAEs[c]	18 (17)	14 (14)
Serious TEAEs in ≥2% of patients in either treatment group	9 (9)	7 (7)
Serious treatment-related adverse events	5 (5)	7 (7)
Anal abscess	5 (5)	5 (5)
Proctalgia	0	1 (1)
Anal inflammation	0	1 (1)
Liver abscess	0	1 (1)

All data reported as number of patients (%)
[a] New fistula, reopening of closed fistula
[b] Fistula discharge in a closed fistula
[c] Defined as any adverse event that at any dose resulted in death, was life-threatening, caused permanent incapacity or disability, resulted in hospital admission or prolonged a hospital stay, or was medically significant

In conclusion, Panes et al considered that "Cx601 might offer patients with Crohn's disease who have treatment-refractory complex perianal fistulas a novel and minimally invasive closure alternative to avoid the need for systemic immunosuppression or surgery."[3] They noted the following limitations to their study:

- younger patients, patients who had previous surgery other than drainage and seton placement, and patients with more than two and three external fistula openings

[f] It was not considered necessary to contact the authors for clarification, given the limited time resources available for this Brief and given that additional information regarding definitions would be unlikely to lead to a conclusion other than that the safety profiles for patients allocated to Cx601 and those allocated to placebo were similar.

were excluded, as were those with other refractory fistula types including rectovaginal or abdominal fistulas (thus results are not applicable to these patients)

- it was not established whether TEAEs were related to Cx601 or to the associated preparation procedures
- Cx601 cells are specifically derived from adipose tissue with different properties to those of mesenchymal stem cells from other tissues such as placenta or bone marrow (thus results cannot extrapolated to mesenchymal cells from other sources).

Panes also commented that their results were provided only up to week 24, with long-term follow-up of the patients to two years underway, and suggested that future studies should assess the safety and efficacy of repeat Cx601 doses.[3] Further data are required to substantiate the longer-term effectiveness of Cx601 in the treatment of Crohn's disease patients with fistulas refractory to standard management options.

Molendijk et al (2015) reported on an RCT (n=21) comparing three locally injected doses of an aMSCT with placebo for refractory perianal fistulising Crohn's disease, following fistula curettage.[2] Dosages were at 1 x 10^7, 3 x 10^7 or 9 x 10^7 cells (groups 1, 2 and 3, respectively) while the placebo group received an injected solution devoid of cells. The primary outcome, fistula healing, was assessed by clinical examination at six, 12 and 24 weeks post-injection. Healing was defined as the absence of discharge and less than two centimetres of fluid collection, the latter determined by MRI at week 12.

Molendijk and colleagues reported that no adverse events were associated with local injections of the aMSCT at any dosing. The only significant finding reported was that at week six, the percentage reduction in the number of draining perianal fistulas was significantly higher in patients treated with aMSCT at a dosing of 3 x 10^7 cells ('Group 2') compared to placebo (86% versus 22%, respectively, p=0.04). At all other follow-up points and dosing regimens, the percentage improvement failed to show a significant difference when compared to placebo. The authors concluded on the basis of their limited success with the therapy that aMSCT 'appeared to promote healing of perianal fistulas'. The authors did not discuss potential limitations of their trial, but small sample size and lack of long-term follow-up are factors of concern. Larger RCTs, possibly with a focus on a comparison between the 3 x 10^7 cells dosing regimen and placebo, are required to inform policy decisions about the use of the aMSCT described by Molendijk et al.[2]

Economic evaluation

No published economic evaluations were identified, nor were the companies of the identified technologies available to provide unpublished data.

Ongoing research

A search of ClinicalTrials.gov identified several active studies of potential relevance (Table 3), but searching the Australian and New Zealand Clinical Trials Registry returned no results.

Table 3 Active clinical trials investigating cellular therapies for the treatment of refractory Crohn's including perianal fistula

Trial name and identifier	Status	Sponsor and country
Autologous Stem Cell Transplantation for Crohn's Disease NCT00692939	Recruiting	University of Pittsburgh, USA Miltenyi Biotec GmbH, Germany
Pilot Study of Stem Cell Transplantation for Children and Young Adults with Refractory Crohn's Disease NCT02225795	Recruiting	TriStar Health, USA
Autologous Unselected Haematopoietic Stem Cell Transplantation for Refractory Crohn's NCT03000296	Recruiting	Beneficência Portuguesa de São Paulo, Brazil
AlloGeneic Human Mesenchymal Stem Cells (hMSC) in PAtients With FistuLizing Crohn's Disease Via PEri-fistula iNjEctions (GALENE) NCT02677350	Recruiting	University of Miami, USA
Autologous Adipose-derived Stem Cells (ASCs) for the Treatment of Perianal Fistula in Crohn Disease: A Pilot Study (ASPEFIC1) NCT02403232	Recruiting	Papa Giovanni XXIII Hospital, Italy
Transplantation of Bone Marrow Mesenchymal Stem Cell in Crohn's Disease NCT01874015	Recruiting	Royan Institute, Iran
Mesenchymal Stem Cell Therapy for the Treatment of Severe or Refractory Inflammatory and/or Autoimmune Disorders NCT01540292	Recruiting	University Hospital of Liege, Belgium
Safety and Efficacy of FURESTEM-CD Inj. in Patients With Moderately Active Crohn's Disease NCT02000362	Recruiting	Kang Stem Biotech Ltd, Korea
A Study to Evaluate the Safety of ALLO-ASC-CD for Treatment of Crohn's Disease NCT02580617	Recruiting	Anterogen Ltd, Korea
Stem Cell Fistula Plug in Perianal Crohn's Disease (MSC-AFP) NCT01915927	Recruiting	Mayo Clinic, USA

Other issues

Panes et al (2016)[3] were funded by TiGenix.

One identified RCT[10] reporting on *haematopoietic* stem cell therapy for refractory Crohn's disease reported that there were 76 serious adverse events among a total of 23 patients allocated to active treatment compared with the control group among whom there were 38 such events. One patient undergoing haematopoietic stem cell therapy died of causes that could not be attributed to any factors pre-existing to the time of study enrolment. Further, the therapy did not result in statistically significant difference in treatment efficacy when compared to the control condition.

TxCell provided the following update in regard to the evaluation of their technology:

"The clinical development of Ovasave, and of the ASTrIA platform in general, is currently on hold, pending (i) validation of the improved manufacturing process; (ii) appropriate funding to finance the clinical development, and (iii) a strategic review. There is no longer a Phase IIb clinical trial ongoing."

This feedback suggests the technology in its current form will be superseded. In its current form, the Ovasave technology appears unlikely to emerge within the Australian or New Zealand healthcare systems. Potential future iterations of the technology may warrant review at a later time.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 4

Total number of Level II studies: 2

Total number of Level IV studies: 2 (including one single case series and one meta-analysis of multiple case series)

Search criteria to be used (MeSH terms)

Crohn Disease; Crohn Disease/complications; Rectal Fistula; Mesenchymal Stem Cell Transplantation; Mesenchymal Stromal Cells; Bone Marrow Transplantation; Transplantation, Homologous; Cells, Cultured; Adipose Tissue; Wound Healing; Humans

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