Biotechnology Journal
www.biotechnology-journal.com

Bringing Stem Cell-Based Therapies for Type 1 Diabetes to the Clinic: Early Insights from Bioprocess Economics and Cost-Effectiveness Analysis

*Cátia Bandeiras, Joaquim M. S. Cabral, Robert A. Gabbay, Stan N. Finkelstein, and Frederico Castelo Ferreira**

Differentiation of pluripotent stem cells (PSCs) into β cells could provide insulin independence for type 1 diabetes (T1D) patients. This approach would reduce the clinical complications that most patients managed on intensive insulin therapy (IIT) face. However, bottlenecks of PSC manufacturing and limited engraftment of encapsulated cells hinder the long-term effectiveness of these therapies. A bioprocess decision-support tool is combined with a disease state-transition model to evaluate the cost-effectiveness of the stem cell-based therapy against IIT. Clinical effectiveness is assessed in quality-adjusted life years (QALYs). Manufacturing costs per patient reduce from $430 000 to $160 000 with optimization of batch size and annual demand. For 96% of the patients, cell therapy improves the quality of life compared to IIT. Cost savings are achieved for 2% of the population through prevention of renal disease. The therapy is cost-effective for 3.4% of patients when a willingness to pay (WTP) of up to $150 000 per QALY is considered. A 75% cost reduction in the cell therapy price increases cost-effectiveness likelihood to 51% at $100 000 per QALY. This study highlights the need for scalable manufacturing platforms for stem cell therapies, as well as to prioritizing access to the therapy to patients with an increased likelihood of costly complications.

1. Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease that destroys β cells. As a result, secretion of insulin by the pancreas and control of glucose levels in the blood are impaired.[1] Disease onset occurs most frequently between 6 and 12 years of age.[2,3] With an estimated population of 1.1 million patients, the economic burden of T1D in the United States is considerable. The total lifetime medical costs of T1D management are $133.7 billion, with a total income loss of $289.2 billion.[4] These patients are insulin dependent and are at an increased risk of related complications, such as amputation, blindness, and kidney failure.[5] Most patients are managed on insulin intensive therapy (IIT) for as long as the clinical complications are not prohibitive.

Therapeutic interventions restoring insulin independence could mitigate related complications and reduce healthcare expenditure. Whole-pancreas transplantation, even when successful, can lead to significant complications. As most patients only require restoration of their β cells, islet cell transplantation is a solution approved in several countries. These cell transplants can require revision due to graft-related complications and lifelong immunosuppression therapy may be needed.[6,7] Strategies to avoid the need for lifelong immunosuppression therapies

C. Bandeiras, Prof. J. M. S. Cabral, Prof. F. C. Ferreira
Department of Bioengineering, iBB—Institute for Bioengineering and Biosciences
Instituto Superior Técnico
Universidade de Lisboa
1049-001, Lisboa, Portugal
E-mail: frederico.ferreira@ist.utl.pt

C. Bandeiras, Prof. J. M. S. Cabral, Prof. F. C. Ferreira
The Discoveries Center for Regenerative and Precision Medicine, Lisbon Campus
Instituto Superior Técnico, Universidade de Lisboa
1049-001, Lisboa, Portugal

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/biot.201800563.

C. Bandeiras, S. N. Finkelstein
Division of Clinical Informatics, Department of Medicine
Beth Israel Deaconess Medical Center
1330 Beacon Street
Brookline, MA 02446, USA

Dr. R. A. Gabbay
Joslin Diabetes Medical Center
Harvard Medical School
One Joslin Place
Boston, MA 02216, USA

S. N. Finkelstein
Institute for Data, Systems and Society
Massachusetts Institute of Technology
50 Ames Street
Cambridge, MA 02139, USA

DOI: 10.1002/biot.201800563

 © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

include the encapsulation of islet and β cells. When these cells are encapsulated prior to transplantation, they become isolated from the host's immune system while still being able to access nutrients and secrete insulin.[8]

The cell supply hurdle could be resolved by functional insulin-secreting cells obtained from directed pluripotent stem cell (PSC) differentiation. Preclinical and early clinical stage research is ongoing, aiming at the implantation of PSC-derived β cells or pancreatic progenitors, differentiated from either human embryonic stem cells (hESCs) or human-induced pluripotent stem cells (hiPSCs). Encapsulated progenitors differentiate in vivo into insulin-secreting β cells.[7,9–12] A clinical concern with these approaches relates to postimplantation time to insulin secretion. Additionally, incomplete PSC differentiation or purification places patients at risk of developing teratomas. Moreover, long and inefficient processes for the expansion of PSCs and differentiation into the pancreatic lineage are cost prohibitive.[11–13] Therefore, approaches suggesting cues for optimization of manufacturing costs, while retaining clinical effectiveness, are desirable.

Stem cell bioprocess economics models have aided in the reduction of manufacturing costs.[14–17] These costs may drive cost-effectiveness analysis for clinical applications. Cost-effectiveness analysis was performed for a possible therapy based on autologous iPSCs-derived β cells. Cost-effectiveness, in comparison to IIT, was achieved by averting complications over an eight-year period following the transplant.[18] Bioprocess economics and cost-effectiveness modeling have been combined for hESCs-derived therapies for T1D. In this work, suspension technologies and a large-scale production strategy are required for cost-effectiveness.[7] While invaluable, these studies show a limited combined assessment of manufacturing and cost-effectiveness. Manufacturing bottlenecks of cell supply, such as differentiation efficiency and downstream processing (DSP) level, were not addressed.

We previously reported a bioprocess economics model,[19] extended here for the expansion and differentiation of PSCs into islet cells. The incorporation of a health economics model of T1D supports optimization of manufacturing and clinical effectiveness. This approach aims at providing input for technological innovation on the manufacturer's side, with the goal of producing cost-effective therapies for restoring insulin independence.

2. Experimental Section

2.1. Case-Study Definition

This work focused on the early health technology assessment of a stem cell-based implantable therapy for T1D, with devices containing PSC-derived islet cells. Each device contains approximately 100 million islet cells.[20] Each patient is transplanted with five devices, for a total final dose per patient of 500 million cells. The first scenario was one patient per batch, five patients per year. Then, a scenario of 50 patients, 250 devices per year, was derived in agreement with a phase I/II clinical trial (NCT02239354). A case where 50 patients per year, 1 patient per batch, are produced was simulated, where several batches are processed in parallel and there was a staggering of the utilization of the purification equipment, aiming at the reduction of costs. These two cases were fresh products and a made-to-order scenario was adopted. Further optimization of utilization of the equipment capacity was performed through a case with 50 patients per year, 10 patients per batch. This strategy aimed at cryopreserved, off-the-shelf therapies.

The early assessment comprised a bioprocess economics model and a disease state cost–utility analysis. The bioprocess economics model was used to calculate the costs of goods (CoGs) of the devices and these CoGs were then linked to the clinical cost-effectiveness through a disease state model comparing stem cell-based therapy with IIT.

2.2. Bioprocess Economics Model Implementation

The bioprocess economics model was reported elsewhere for mesenchymal stem/stromal cells.[19] Briefly, this model encompassed the expansion of PSC in vials from a working cell bank (WCB). Cells from WCB vials were expanded for four passages. The model was expanded to include cell aggregation and differentiation protocols as previously reported for T1D. Cost and mass balance inputs drove the calculation of the total CoGs per dose, as well as the CoGs breakdown per resource and per process stage (Table S1 and Supporting Model Equations, Supporting Information). The number of cells per PSC bank and the cost per million cells were derived from published estimates.[21] The PSC expansion parameters were an average of a range of scalable expansion runs of MCB and WCB PSCs in 2D cell culture flasks (T-flasks and cell factories).[12] A differentiation yield of PSCs into islet cells of 80% was assumed based on a range of values from differentiation protocols.[9] We simulated a DSP strategy using magnetic-activated cell sorting (MACS). This technique was previously reported for the purification of β cells from a complex mixture[22] as well as for the positive selection of pancreatic and endoderm progenitors derived from stem cells.[23–25] A DSP yield of 20% was used for model runs, based on the yield from the purification of β cells from cadaveric pancreatic donors[22] (Figure S1 and Table S1, Supporting Information). The reagent costs were adapted from the several media formulations used for cell expansion, aggregation, and differentiation (Table S1, Supporting Information). The facility dimensions were varied in order to supply the annual demands and batch sizes.[14–16,26,27] A nominal batch failure rate at the release testing stage of 30% was included, accounting for the several different batch failure step rates (banking, expansion, differentiation, and release testing). This estimate was provided for the manufacturing of PSC-derived islet cells after discussions with experts. The costs of failed batch runs were spread out by the total passed runs. Additionally, a sensitivity analysis to evaluate the reduction in CoGs caused by changing specific inputs to the best possible case was performed for the three manufacturing strategies. The best-case parameter choice is depicted in the Supporting Methods, Supporting Information.

© 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

2.3. Disease State Model Implementation

A discrete state-transition Markov model for the cost-effectiveness of β cell transplantation for T1D was employed. The model was implemented in Python for compatibility with the bioprocess model and slightly modified from published models.[5,7,18,28] The comparator therapy was IIT. In this model, five states were defined for the β cell transplant model: full insulin independence, partial graft function without complications (insulin dependent, but producing other relevant factors for glucose control), graft failure without complications, diabetes-related complications (after graft failure), and death (Figure S2, Supporting Information). The IIT arm had three states: IIT without complications, diabetes-related complications, and death. A 20-year follow-up was modeled. Costs and utilities, with utilities representing a score in the 0–1 range for the quality of life of a year associated with each health state, were computed every year and discounted at an annual rate of 3%.[7,28,29] Initially, a patient undergoing IIT had a utility weight of 0.71, in agreement with patients with hypoglycemia unawareness. A patient with partial graft function had a utility of 0.81, as a T1D patient without complications, but requiring insulin administration. Patients with full graft function had a utility of 0.91, similar to healthy young adults.[5,28] Note that the model assumed equivalent clinical effectiveness and graft failure rates to cadaveric islets. In the case of graft failure, a new transplant may be performed to ensure long-term insulin independence.[7,28] As a modification from previous cost-effectiveness analyses approaches in the field, we assumed that no immunosuppression was required for these transplants. The lack of immunosuppression requirement is related to encapsulation that protects the cells from both alloimmune and autoimmune attack.[5,18,28] The model was run considering a sample of 1000 hypothetical patients, with probabilities of complications and state transition sampled from data on transplantation of cadaveric donor islets.

It was considered that patients could suffer complications from five main groups: hypoglycemia, cardiovascular, neuropathy, nephropathy, and ophthalmological.[30] Each complication was computed with increased medical costs and a utility decrement per patient of up to −0.29.[31,32] Yearly costs and quality-of-life scores (i.e., utility weights) associated with each state were computed. Moreover, patients could move through states according to event probabilities. All costs were presented and, when required, adjusted to 2017 USD using the Consumer Price Index.[33] The key assumptions of the health economics study are depicted in Table S2 (Supporting Information). After the follow-up period, the total direct medical costs were computed, as well as a sum of the utilities per year yielding the total quality-adjusted life-years (QALYs). The cost-effectiveness of the new treatment was assessed as an incremental cost-effectiveness ratio (ICER), a ratio of the total difference in costs to the difference in QALYs between the two therapies. Stem cell-based therapy was cost-effective if it was below a given willingness to pay (WTP) threshold in cost per QALY. In order to stratify the patients who could benefit the most from stem cell-based therapy, due to the type of complications averted using stem cell-based therapy in comparison with IIT, the number of patients with complications averted and type of complications averted in a typical WTP threshold were evaluated as well.

3. Results

3.1. Increase of Annual Demand and Batch Size Offer Bioprocess Cost Savings

For the annual demand of five patients, and strategy of 1 patient per batch, 10 million WCB PSCs were required to start the PSC expansion process. After expansion, 4.79 billion cells were obtained, with an estimated 2.87 billion islet cells. The purification process yielded 767 million islet cells. The total processing time per batch was 42 days. The total CoGs per stem cell-based device were $85 446, yielding a total CoGs per patient of $427 231. Increasing the demand to 50 doses per year, 1 patient per batch, reduced the CoGs per stem cell-based device to $71 763 and the CoGs per patient to $358 818. The 19% decrease in cost with the increase in the annual demand was due to a more efficient distribution of indirect costs across multiple batches processed in parallel.

We estimated that only 25% of the expansion capacity per incubator, 30% of the differentiation capacity per incubator, and 14% of the MACS sorting capacity per equipment were utilized per batch. In order to allow the more efficient use of the equipment, 65 million PSCs from the WCB were seeded to start the process. A batch consisting of cells from a single MACS equipment yielded enough cells for ten patients. The 50 patients per year, 10 patients per batch process, resulted in CoGs per stem cell-based device of $32 744 (CoGs per patient of $163 720). These costs represent a 54% reduction from the 50 patients per year, 1 patient per batch scenario (**Figure 1**A). As manufacturing costs of cadaveric islets per patient are in the order of $80 000, these manufacturing strategies still resulted in higher manufacturing costs per patient than cadaveric islets.[34]

In the 5 patients per year, 1 patient per batch setting, 46% of costs were attributed to the reagents (expansion and differentiation media, harvesting and purification reagents, final formulation buffers). This was, by far, the highest contribution in direct process costs (banking costs are 4% of the total, consumables account for 3%, while quality controls account for 8% of the total costs per dose). Regarding the indirect costs, the labor costs were 32% of the total costs per dose and the facility-associated costs (building and equipment operational and depreciation costs) contributed to 8% of the total costs. The increase in annual demand to 50 patients led to a noticeable reduction in the indirect costs contribution per dose as the labor costs were 9% of the total costs per dose and facility costs were 3% of these costs. This was a result of parallel processing of different batches, spreading the indirect costs over several batches. It is worthwhile noticing that the absolute values of direct costs per dose (banking, consumables, reagents, and quality controls) increased in the 50 patients per year case. This was a result of the inclusion of the costs of failed batch runs. For 50 patients per year, increasing the batch size to 10 patients further decreased the indirect costs contribution, with labor accounting for 9% of costs and the facility for 2% of the costs. The reagent costs accounted for 82% of the total dose costs (Figure 1B). Regarding the process stages, the main share of costs was attributed to the differentiation

© 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

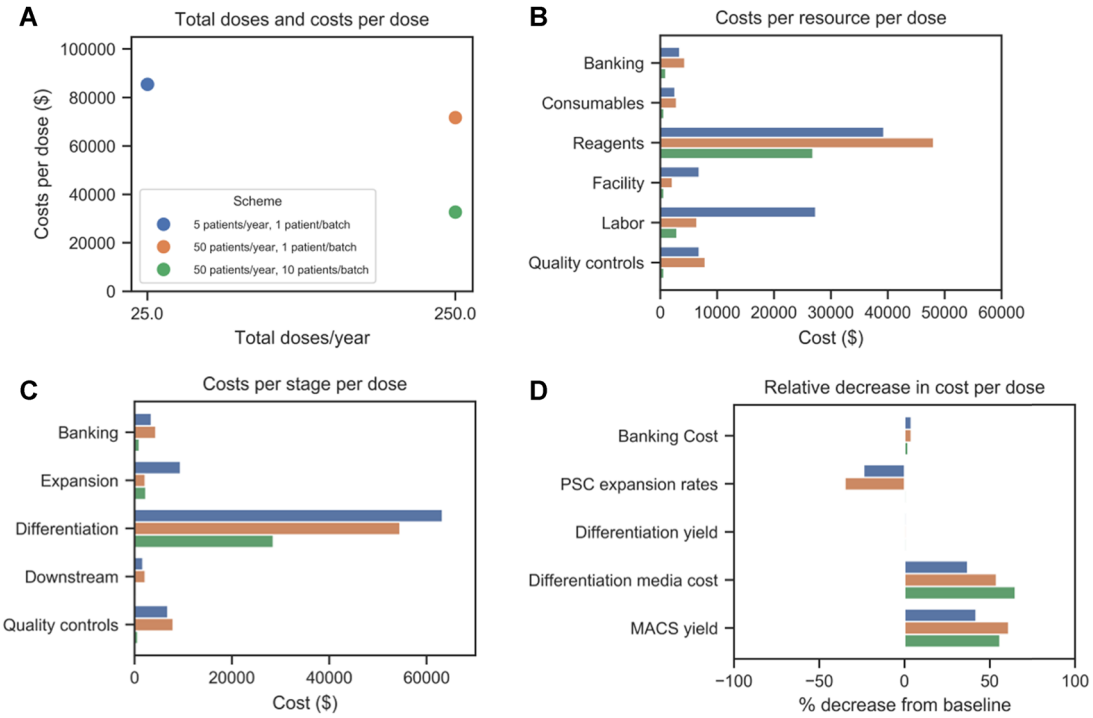

Figure 1. Efficiency of facility utilization, media costs, and downstream process yields are key factors to optimize toward economical manufacturing of stem cell-derived β cell therapies. A) An increase in annual demands and the number of patients per batch yield considerable cost savings in the manufacturing of stem cell-based β cell devices. Costs of manufacturing vs the number of doses produced per year. Each patient received five doses per transplant. B) Breakdown of costs per dose of each resource. Reagents (culture media, harvesting, and DSP buffers) dominate the cost breakdown, followed by labor, release testing quality controls, and facility and equipment depreciation. C) Breakdown of costs per process stage. The differentiation from PSC into β cells dominates the costs, followed by expansion, quality controls, and DSP. D) Sensitivity analysis of the total costs per dose when improving process parameters to a best-case scenario. The reduction of differentiation media costs and the increase in the purification yield promote the largest cost reductions.

stage for every process configuration (74–87% of the total costs per dose). The differentiation stage involved media exchange daily or every other day, resulting in large volumes of culture media spent.[10,11] The costs of generation of banking vials accounted for 3–6% of the total cost breakdown. DSP accounted for 1–3% of the costs as the cell volumes were consistent with the limitations of the MACS equipment. The cost contribution of expansion was 3–11% of the total costs, with the costs decreasing with the increased annual demand and batch size, as these costs were spread over a higher number of doses (Figure 1C).

3.2. Media Costs and Downstream Yield are Key Factors to Optimize

Figure 1D illustrates the changes in CoGs in response to the change in input parameters to their best-case values. When increasing the expansion growth rates to the best possible case, the CoGs for the 1 patient per batch case increased by 24–35%. For the process with 10 patients per batch, a minor cost reduction of 1% was achieved. The increases in expansion growth rates resulted in a lower number of WCB cells necessary to seed the expansion stage to reach full incubator capacity. Under the increased expansion yields, 7.5 million cells from the bank were required to start expansion, instead of 10 million in the baseline case for 1 patient per batch. For 10 patients per batch, the number of WCB cells required was reduced from 35 million cells to 25 million cells. However, an increased expansion rate led to an excess of production, accompanied by an increased expenditure in consumables and reagents. Consequently, the costs were not reduced and may even have increased. The increase in expansion rates would be interesting as a means to increase the number of cells expanded from the same initial number of PSC. This could increase the number of devices produced per batch, enabling an increase in the scale of production and the decrease in the costs of goods per batch.

The differentiation yield was increased to 95% as a best-case scenario but its effects were negligible as the baseline case operated with a considerably high differentiation yield of 80%. However, as reagent costs and the differentiation unit operation were major cost contributors, the reduction in the differentiation media costs had a major impact as CoGs per device were reduced by 37–65%. Assuming the best-case DSP scenario, for which the reported MACS yield was 86%, the reductions in the cost per dose were 42–61%. Therefore, the optimization of DSP systems (assuming consistent differentiation yields of PSCs into islet cells), would be a key strategy to increase batch size and reduce costs per device. Cell vials' sourcing cost was also evaluated in this sensitivity analysis. The reduction to a best-case cost of $375 per million cells led to a small decrease in the costs per dose of 2–4%.

© 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. Mean and confidence intervals (CIs) for the costs and QALYs for the two T1D therapeutic options calculated using the disease state-transition model.

	20-year costs (mean and 95% CI)	QALYs (mean and 95% CI)
Insulin	$310 425 ($138 231–$369 572)	9.59 (4.40–10.88)
Islet cell device	$1 241 957 ($922 922–$2 165 641)	13.32 (8.39–13.94)

By applying the reported improvements in DSP yield and media costs to the cheapest initial scenario (50 patients per year, 10 patients per batch), the CoGs per dose would decrease to approximately $12 000 per dose, with a total manufacturing cost per patient of $60 000. In this fashion, the CoGs per patient for stem cell-based devices would be lower than for cadaveric islets.

3.3. Cost-Effectiveness of the Cell-Loaded Devices Is Related to Prevention of Complications

The bioprocess economics model results provided inputs for the price per patient of stem cell-based devices needed for the transplantation arm of the disease state model. Considering the manufacturing strategy of 50 patients per year, 10 patients per batch, the final price per transplant per patient was assumed to be $650 000 (such that CoGs if 25% of the final price).[35] The stem cell-based therapy yielded improved life outcomes. The model calculated an increase of 3.73 QALYs per patient, on average, in comparison with IIT, over a 20-year timespan. However, the transplant is, overall, a more costly treatment due to high upfront costs. Direct medical costs over a 20-year timespan were, on average, four times higher than for IIT (**Table 1**). Each patient underwent between one and three transplantations in the timespan of the analysis.

Figure 2A depicts the individual QALYs and costs increments analysis using the stem cell-based therapy vs IIT. 96.4% of the patients had higher QALYs with stem cell-based therapy. The transplant was a cost-saving alternative for only 1.6% of the patients as they also showed lower direct medical costs in comparison with IIT. For these patients, end-stage renal disease (ESRD) was averted with the transplantation, irrespective of the occurrence of other complications (Table S3, Supporting Information).

The cost-effectiveness for the patients with higher cost and QALYs under the transplantation scheme is dependent on the ICER and the WTP threshold. At a WTP threshold of $50 000 per QALY, the stem cell-based therapy is cost-effective for only 1.9% of the patients. Within this group, the correlation with the type of complications averted by cell therapy was not as pronounced. For 75% of the patients for whom cost-effectiveness was achieved at $50 000 per QALY, more than one complication was averted by the transplantation of stem cell-based devices (Table S3, Supporting Information). The complication averted with the highest frequency was ESRD (35.2%), followed by congestive heart failure (CHF) (14.8%). At the WTP threshold of $50 000 per QALY, the probability of cost efficiency is only marginally affected by the final price of the stem cell therapy. While the cost-effectiveness probability for the 50 patients per year, 10 patients per batch, at this threshold, is low, it represents an improvement from the manufacturing strategies with 1 patient per batch. The final prices per transplant per patient, calculated considering that the manufacturing costs in Figure 1 represent 25% of the final price, are $1.7 million for the 5 patients per year scenario and $1.45 million for the 50 patients per year case. For these two scenarios, the transplant would not be cost-effective for any patient at the $50 000 per QALY threshold.

Considering the $100 000 per QALY, the intervention is cost-effective for about 3.4% of the patients in the baseline scenario. At such ICER, the price of the cell-loaded device plays a more

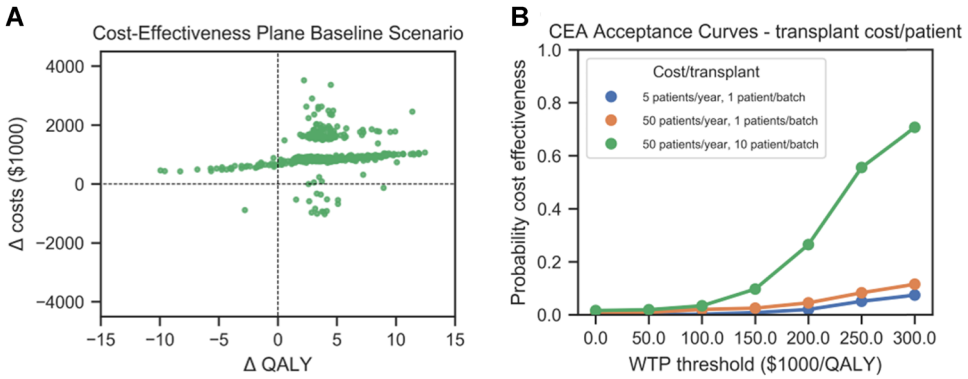

Figure 2. Cost-effectiveness of β cell transplants is sensitive to cost-effectiveness acceptance thresholds. A) Cost-effectiveness acceptance plane after a 20-year follow-up period from the transplant, assuming a price per transplant of $650 000 (considering that the manufacturing costs per patient of the 50 patients per year, 10 patients per batch scheme represent 25% of the final transplant price per patient). Points are 1000 randomly sampled individual patients. Differences in cost and QALYs show that, for most patients, the transplant is more effective in providing a better quality of life, but generally with higher direct medical costs. B) Cost-effectiveness acceptance probability curve relative to the WTP thresholds employed by the payer for transplants using devices manufactured under the 5 patients per year, 1 patient per batch ($1.7 million final transplant price), 50 patients per year, 1 patient per batch ($1.45 million final transplant price) and the 50 patients per year, 10 patients per batch ($650 000 final transplant price) strategies. Probabilities are calculated as the ratio of the number of patients with an ICER for stem cell-based therapy below each WTP threshold by the total number of patients.

© 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

significant role. For the 1 patient per batch manufacturing scenarios, the cost-effectiveness probability at $100 000 per QALY ranged from 0.2% (5 patients per year) to 2% (50 patients per year). A total of 60% of patients had complications averted by the utilization of stem cell-based devices, with the most commonly averted complications being ESRD, gangrene, and CHF (avoided in 13.3% of patients for each complication). At $150 000 per QALY, 13.2% of the patients show cost-effectiveness with the transplant for the 50 patients per year, 10 patients per batch case. At this threshold, cost-effectiveness probabilities for the other scenarios are 0.8% (5 patients per year, 1 patient per batch) and 2.5% (50 patients per year, 1 patient per batch). The most commonly averted complications are CHF (25.4% of patients) and nonproliferative retinopathy (15.8% of patients). A total of 60% of the patients with ICER between $100 000 and $150 000 per QALY had complications averted. Therefore, at high WTP thresholds, the avoidance of high-cost complications gradually became less relevant for ensuring cost-effectiveness. For the manufacture strategies of 1 patient per batch, the cost-effectiveness probability was still very low at high WTP thresholds of $300 000 per QALY, with only 10% of the patients for whom the transplant would be cost-effective in comparison with IIT. The 50 patients per year, 10 patients per batch strategy indicates, at high WTP thresholds, a vast improvement from the 1 patient per batch strategies as 70% of patients would benefit from a cost-effective transplant at the $300 000 per QALY threshold (Figure 2B).

A sensitivity analysis was performed to identify strategies to increase the likelihood of cost-effectiveness. At $50 000 per QALY, a reduction in the transplant costs between 25% and 75% for 50 patients per year, 10 patients per batch strategy would increase the probability of cost-effectiveness to 2.2–3.1% of the patient population, respectively. At the $100 000 per QALY threshold, a more relevant improvement in cost-effectiveness probability to up to 51.7% of the patients was achieved (**Figure 3**A).

At $50 000 per QALY, further reductions in the probability of diabetes-related complications by a functional graft increased the probability of cost-effectiveness to only 2.4%. For the higher thresholds, the differences due to further reductions in graft failure probabilities remained nonsignificant. This was a considerably more modest increase than provided by the reduction of manufacturing costs (Figure 3B). The final analyzed parameter was the annual graft failure probabilities. At $100 000 per QALY, a 75% reduction in the annual graft failure probabilities does not increase the cost-effectiveness probability (Figure 3C). The differences between groups became relevant only at the threshold of $300 000 per QALY, for which a reduction of 75% in the probability of complications increased the cost-effectiveness probability to 81.8%. Overall, stem cell-based therapy can further benefit from cost reductions to ensure cost-effectiveness and robustness to reimbursement prices.

4. Discussion

The modeling results provide support for long-term cost-effectiveness of stem cell-based devices as therapies for T1D, given that the estimated possible price per transplant with the

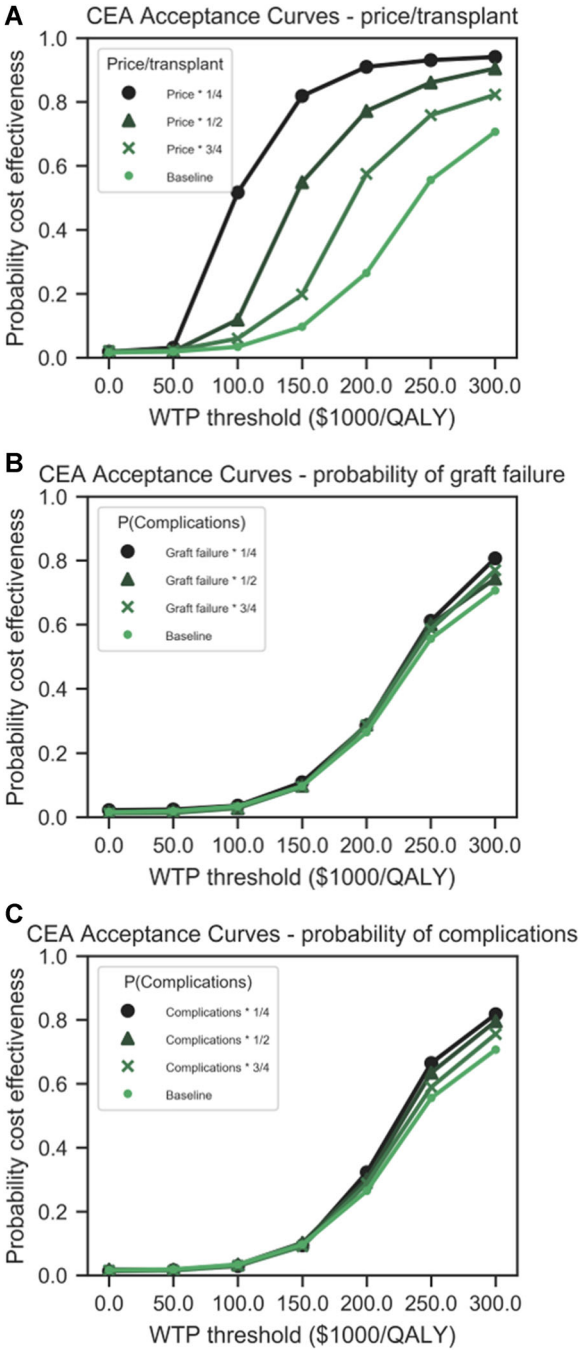

Figure 3. Further optimization of cell-loaded device costs is key for improved cost-effectiveness while retaining clinical effectiveness. Cost-effectiveness acceptance curves where key health economics modeling parameters are reduced by 25%, 50%, and 75% of the nominal value, assuming a baseline price per patient of $650 000 (equivalent to the 50 patients per year, 10 patients per batch strategy). Probabilities are calculated as the ratio of the number of patients with an ICER for stem cell-based therapy below each WTP threshold by the total number of patients. A) Price per patient. B) Probability of diabetes-related complications when the graft is functional. C) Probability of graft failure.

© 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

manufacturing scenarios simulated in the bioprocess economics model ($650 000–$1.7 million) is significantly reduced. While the direct medical costs in this study differ from the previously published literature, our conclusions are analogous to those of earlier health technology assessments of stem cell-based β cell devices.[7,18]

In order to reduce CoGs per dose, a scale-up approach, where batches have high numbers of doses, is desired. However, a key limiting factor in the scaling-up production of cell therapies is the DSP.[15,17,27] In our model, the current low DSP yield reported for MACS purification of islet cells limited the batch size as a theoretical maximum of just above 5 billion differentiated islet cells (i.e., enough doses for ten patients) can be obtained per MACS cycle.[22,26,27] Increasing the MACS yield to values reported for affinity purification processes for pancreatic progenitors and definitive endoderm[23–25] yielded significant cost-savings per dose. Current clinical trials do not employ an affinity purification step and encapsulate the pancreatic progenitors assuming that a very high differentiation efficiency is sufficient to minimize the occurrence of teratomas. This strategy would reduce costs and allow higher batch sizes. However, recent animal studies show that teratomas may occur in stem cell-based devices and that a purification step is advisable for safety.[36] In order to overcome the scalability and yield limitations of MACS, economic assessment of other DSP systems evaluated for PSCs and PSC-derived differentiated cell types, such as aqueous two-phase separation and tangential flow filtration,[17,37] could be a future strategy to increase the annual demand and batch size without compromising the facility footprint.

The total costs of manufacturing per patient obtained with the different strategies are above the range presented in a recent study on the CoGs modeling of stem cell-derived devices containing pancreatic progenitors.[7] It is important to note that the mentioned study differs from the analysis presented in this work in three key points: the stem cell-based devices contain pancreatic progenitors, with a higher differentiation yield and a faster differentiation process than terminally differentiated β cells, it does not take into account the contribution of the cell bank vials in the process, and does not explicitly address DSP bottlenecks. However, pancreatic progenitor-based devices might take longer to secrete insulin in vivo than β cell-based devices.[38] As a four- to five-week process to obtain terminally differentiated islets was simulated, differentiation costs dominate the cost breakdown. The costs of differentiation can be mitigated by the development of more efficient directed differentiation and media exchange protocols at a larger scale. The scalability of the process to 3D suspension platforms, such as spinners[9,11,39] and bioreactors,[40,41] either in aggregate or microcarrier-based platforms, could improve both the expansion and differentiation rates and yields by providing a more similar environment to the native niche, combined with better metabolite and growth factor control.[36,42–44]

While the stem cell-based therapy would bring an added quality of life to most patients, the transplantation has very high upfront costs in comparison with the continuous administration of insulin. The finding that the therapy would be cost saving for patients for whom ESRD is avoided is consistent with the current clinical development of devices allowing direct vascularization for the treatment of patients with a high risk of ESRD.[45,46] The development of predictive models of diabetes-related complications[47,48] would help optimize the allocation of resources of these high-value, high-cost therapies under budget limitations. The cell-loaded device price is one of the critical factors influencing the probability of cost-effectiveness, and increased likelihood of reimbursement by healthcare payers in budget-constrained scenarios. For the parameter range evaluated in the sensitivity analysis, this is particularly noticeable at a threshold of $100 000 per QALY. A previous study, focused on the United Kingdom healthcare system and using a headroom method approach, recommended reimbursement at a threshold of £20 000 ($26 089) per QALY for the new therapy as cost-effective.[18] For that threshold and the manufacturing costs calculated by our model, the new therapy would only be cost-effective for up to 2% of the patients, eliciting the need for reduction of complications and associated clinical costs. A similar ratio is noticed at a threshold of $50 000 per QALY as well. This fact elicits the need for even larger cost reductions associated with the transplantation for the prospective therapy to be adopted over insulin under more strict healthcare spending scenarios. The present study was conducted from a US payer perspective, a market for which cost-effectiveness does not determine recommendations for reimbursement by each healthcare payer. Still, most of the interventions recommended by the American Diabetes Association were cost-effective at $50 000 per QALY.[49] The use of our analysis, updated with country-specific healthcare utilization costs, would be particularly useful for decisions in markets for which cost-effectiveness analysis is a key factor of recommendation for reimbursement.

This study aimed at providing cues for initial manufacturing strategies and how the manufacturing costs and the treatment cost-effectiveness influence each other. The study is limited to the scale of manufacturing and reports costs per run in order to access key bottlenecks in the process. The process costs are dependent on the scale of the operation and this tool can be used for the design processes of facilities of different dimensions. Design process considerations include not only scale but also decisions concerning centralized vs decentralized manufacturing schemes.[7] Additionally, supply chain considerations that will increase the costs are not included in this analysis. Finally, the lack of clinical trial data on efficacy and effectiveness is also a model limitation. The first clinical trials in this field are still in progress. However, the findings of this work create an initial framework for optimizing manufacturing of stem cell-based devices aiming at improved health outcomes and reduced costs.

This study demonstrates that manufacturing parameter optimization would result in costs in the range of cadaveric islets for transplantation, given a more optimal utilization of manufacturing resources. Moreover, cost-effectiveness at WTP thresholds between $50 000 and $150 000 per QALY could be improved by a reduction of cell-loaded device costs, together with the reduction of diabetes-related complications and sustainable, long-term cell-loaded device engraftment. The reduction of cell-loaded device costs of manufacturing is related to more optimal PSC expansion, differentiation, and purification protocols. The findings suggest an increased need for

© 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

research in the field in order to provide safe, cost-effective, curative approaches for T1D.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The authors acknowledge funding from the Institute for Bioengineering and Biosciences (UID/BIO/04565/2013) and Programa Operacional Regional de Lisboa 2020 (Project no. 007317) and also through the project PRECISE (PAC-PRECISE-LISBOA-01–0145-FEDER-016394). C.B. acknowledges Fundação para a Ciência e a Tecnologia (FCT) for the Ph.D. fellowship PD/BD/105868/2014. Feedback in pluripotent stem cell bioprocessing from Dr. Tiago Fernandes, Ana Rita Gomes, and Diogo Nogueira (Stem Cell Engineering Research Group—Instituto Superior Tecnico) and Jerome Ritz, M.D. (Dana-Farber Cancer Institute) is also acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioprocess economics, health economics, pluripotent stem cells, type 1 diabetes

Received: December 10, 2018
Revised: April 21, 2019
Published online: July 8, 2019

[1] S. A. Paschou, N. Papadopoulou-Marketou, G. P. Chrousos, C. Kanaka-Gantenbein, *Endocr. Connect.* **2018**, *7*, R38
[2] M. Beckstrand, Walden Dissertations and Doctoral Studies, Walden University 2015.
[3] N. H. Cho, J. E. Shaw, S. Karuranga, Y. Huang, J. D. da Rocha Fernandes, A. W. Ohlrogge, B. Malanda, *Diabetes Res. Clin. Pract.* **2018**, *138*, 271.
[4] B. Tao, M. Pietropaolo, M. Atkinson, D. Schatz, D. Taylor, *PLoS One* **2010**, *5*, e11501.
[5] J. Beckwith, J. A. Nyman, B. Flanagan, R. Schrover, H.-J. Schuurman, *Clin. Transplant.* **2012**, *26*, 23.
[6] R. Aathira, V. Jain, *World J. Diabetes* **2014**, *5*, 689.
[7] K. Wallner, R. G. Pedroza, I. Awotwe, J. M. Piret, P. A. Senior, A. M. J. Shapiro, C. McCabe, *BMC Endocr. Disord.* **2018**, *18*, 6.
[8] T. J. Kieffer, K. Woltjen, K. Osafune, D. Yabe, N. Inagaki, *J. Diabetes Invest.* **2018**, *9*, 457.
[9] A. D. Agulnick, D. M. Ambruzs, M. A. Moorman, A. Bhoumik, R. M. Cesario, J. K. Payne, J. R. Kelly, C. Haakmeester, R. Srijemac, A. Z. Wilson, J. Kerr, M. A. Frazier, E. J. Kroon, K. A. D'Amour, *Stem Cells Transl. Med.* **2015**, *4*, 1214.
[10] J. R. Millman, C. Xie, A. VanDervort, M. Gürtler, F. W. Pagliuca, D. A. Melton, *Nat. Commun.* **2016**, *7*, 11463.
[11] F. W. Pagliuca, J. R. Millman, M. Gürtler, M. Segel, A. VanDervort, J. H. Ryu, Q. P. Peterson, D. Greiner, D. A. Melton, *Cell* **2014**, *159*, 428.
[12] T. C. Schulz, H. Y. Young, A. D. Agulnick, M. J. Babin, E. E. Baetge, A. G. Bang, A. Bhoumik, I. Cepa, R. M. Cesario, C. Haakmeester, K. Kadoya, J. R. Kelly, J. Kerr, L. A. Martinson, A. B. McLean, M. A. Moorman, J. K. Payne, M. Richardson, K. G. Ross, E. S. Sherrer, X. Song, A. Z. Wilson, E. P. Brandon, C. E. Green, E. J. Kroon, O. G. Kelly, K. A. D'Amour, A. J. Robins, *PLoS One* **2012**, *7*, e37004.
[13] D. Cyranoski, *Nature* **2018**, *555*, 428.
[14] A. S. Simaria, S. Hassan, H. Varadaraju, J. Rowley, K. Warren, P. Vanek, S. S. Farid, *Biotechnol. Bioeng.* **2014**, *111*, 69.
[15] S. Hassan, A. S. Simaria, H. Varadaraju, S. Gupta, K. Warren, S. S. Farid, *Regener. Med.* **2015**, *10*, 591.
[16] M. Jenkins, J. Bilsland, T. E. Allsopp, S. V. Ho, S. S. Farid, *Biochem. Eng. J.* **2016**, *108*, 84.
[17] C. L. Darkins, C.-F. Mandenius, *Chem. Eng. Res. Des.* **2014**, *92*, 1142.
[18] P. R. Archibald, D. J. Williams, *Regener. Med.* **2015**, *10*, 959.
[19] C. Bandeiras, J. M. Cabral, S. N. Finkelstein, F. C. Ferreira, *Regen. Med.* **2018**, *13*, 917.
[20] V. So, L. Martinson, C. Green, M. Scott, M. Zamarripa (ViaCyte Inc.) *US9526880B2*, 2014.
[21] E. Neofytou, C. G. O'Brien, L. A. Couture, J. C. Wu, *J. Clin. Invest.* **2015**, *125*, 2551.
[22] G. A. Martens, V. DePunt, G. Stangé, *J. Tissue. Eng. Regen. Med.* **2018**, *12*, e171.
[23] C. Davenport, U. Diekmann, O. Naujok, *J. Vis. Exp.* **2016**, *109*, 53655.
[24] K. F. Cogger, A. Sinha, F. Sarangi, E. C. McGaugh, D. Saunders, C. Dorrell, S. Mejia-Guerrero, Y. Aghazadeh, J. L. Rourke, R. A. Screaton, M. Grompe, P. R. Streeter, A. C. Powers, M. Brissova, T. Kislinger, M. C. Nostro, *Nat. Commun.* **2017**, *8*, 331.
[25] H. Liu, H. Yang, D. Zhu, X. Sui, J. Li, Z. Liang, L. Xu, Z. Chen, A. Yao, L. Zhang, X. Zhang, X. Yi, M. Liu, S. Xu, W. Zhang, H. Lin, L. Xie, J. Lou, Y. Zhang, J. Xi, H. Deng, *Cell Res.* **2014**, *24*, 1181.
[26] M. J. Jenkins, S. S. Farid, *Biochem. Eng. J.* **2018**, *137*, 192.
[27] B. D. Weil, M. J. Jenkins, S. Uddin, D. G. Bracewell, D. Wellings, S. S. Farid, F. Veraitch, *Regener. Med.* **2017**, *12*, 397.
[28] K. Wallner, A. M. J. Shapiro, P. A. Senior, C. McCabe, *BMC Endocr. Disord.* **2016**, *16*, 17.
[29] A. E. Attema, W. B. F. Brouwer, K. Claxton, *Pharmacoeconomics* **2018**, *36*, 745.
[30] J. Zhu, P. Kahn, J. Knudsen, S. N. Mehta, R. A. Gabbay, *Diabetes Technol. Ther.* **2016**, *18*, 625.
[31] J. Smith-Palmer, J. Bae, K. Boye, K. Norrbacka, B. Hunt, W. Valentine, *Clin. Outcomes Res.* **2016**, *8*, 559.
[32] P. McEwan, H. Bennett, J. Fellows, J. Priaulx, K. Bergenheim, *PLoS One* **2016**, *11*, e0162441.
[33] A. Dunn, S. D. Grosse, S. H. Zuvekas, *Health Serv. Res.* **2018**, *53*, 175.
[34] S. Moassesfar, U. Masharani, L. A. Frassetto, G. L. Szot, M. Tavakol, P. G. Stock, A. M. Posselt, *Am. J. Transplant.* **2016**, *16*, 518.
[35] R. Grant, M. Curtis, M. Brown, *Bioprocess Int.* **2015**, *13(S6)*.
[36] R. Sambathkumar, A. Migliorini, M. C. Nostro, *Physiology* **2018**, *33*, 394.
[37] B. Cunha, R. J. S. Silva, C. Correia, A. Koshkin, P. M. Alves, M. Serra, C. Peixoto, M. J. T. Carrondo, *J. Membr. Sci.* **2017**, *542*, 399.
[38] T. Robert, I. DeMesmaeker, G. M. Stangé, K. G. Suenens, Z. Ling, E. J. Kroon, D. G. Pipeleers, *Stem Cell Rep.* **2018**, *10*, 739.
[39] C. C. Miranda, T. G. Fernandes, M. M. Diogo, J. M. S. Cabral, *Biotechnol. J.* **2016**, *11*, 1628.
[40] A. L. Rodrigues, C. A. V. Rodrigues, A. R. Gomes, S. F. Vieira, S. M. Badenes, M. M. Diogo, J. M. S. Cabral, *Biotechnol. J.* **2019**, *14*, 1800461.

 © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

[41] S. M. Badenes, T. G. Fernandes, C. C. Miranda, A. Pusch-Klein, S. Haupt, C. A. Rodrigues, M. M. Diogo, O. Brüstle, J. M. Cabral, *J. Chem. Technol. Biotechnol.* **2017**, *92*, 492.
[42] Q. Zhou, D. A. Melton, *Nature* **2018**, *557*, 351.
[43] Y. Y. Lipsitz, C. Woodford, T. Yin, J. H. Hanna, P. W. Zandstra, *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 6369.
[44] H. M. Shahjalal, A. Abdal Dayem, K. M. Lim, T.-I. Jeon, S.-G. Cho, *Stem Cell Res. Ther.* **2018**, *9*, 355.
[45] P. A. Senior, J. H. Pettus, *Diabetic Med.* **2019**, *36*, 297.
[46] D. Ilic, *Regener. Med.* **2018**, *13*, 361.
[47] A. J. Karter, E. M. Warton, K. J. Lipska, J. D. Ralston, H. H. Moffet, G. G. Jackson, E. S. Huang, D. R. Miller, *JAMA Intern. Med.* **2017**, *177*, 1461.
[48] K. R. Marino, R. L. Lundberg, A. Jasrotia, L. S. Maranda, M. J. Thompson, B. A. Barton, L. C. Alonso, B. U. Nwosu, *PLoS One* **2017**, *12*, e0176860.
[49] Y. Zhong, P.-J. Lin, J. T. Cohen, A. N. Winn, P. J. Neumann, *Value Heal.* **2015**, *18*, 308.

 © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim