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Review Article

Towards a Mass Customisation Platform for the Biomanufacturing of Gene and Cell Therapy Products

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Abstract

The recent FDA approval of CAR-T cell therapy products has generated much excitement in the field, but also met with some reservation due to their hefty price tags. Because cell therapy products are living tissues that need to be individualized to the patients to prevent host immune response, traditional manufacturing practice for biopharmaceutics cannot be readily adopted. One way in which economy of scale could be achieved for cell therapy products is through a mass customisation platform, which is a manufacturing technique that combines the flexibility of custom-made products with the low unit costs of mass production. In this perspective article, we outline a mass customization platform as a mean to achieve economies of scale and product personalization for the biomanufacturing of patient-specific gene and cell therapy products. To help illustrate this concept, we compared Vistaprint's approach to mass customization of business cards as a real-life example in platform design.

INTRODUCTION

The recent FDA approval of two autologous chimeric antigen receptor (CAR) T-cell therapy products [1], marked the beginning of a new era for the field of gene and cell therapy. This comes nearly 30 years after the first gene therapy trial for the treatment of adenosine deaminase deficiency [2]. The news was not only met with much excitement in the field, but also generated a renewed sense of optimism for more complex cell therapies to follow. However, given the rapid timeline of clinical development for Kymriah and Yescarta, considerations for robust, scalable, industrialised manufacturing was not fully explored. At hefty price tags of $373,000 and $475,000 USD respectively, these CAR T-cell therapies are currently reserved for relapsing or refractory diseases when second- or third-line treatments fail [3]. While there is some tolerance for higher pricing of these first-generation technologies, these prices will not be sustainable in the long run as patient demand increases. With the commercial product coming ahead of the manufacturing capabilities, a host of issues exists, including lack of automation, outdated analytics, and an immature supply chain. Now the challenge for the gene and cell therapy field is to develop efficient and scalable manufacturing strategies that can expand cells clinically relevant quantities reliably and cost effectively.

Unlike small molecules and biologics, cell therapy products are living tissues that need to be patient-matched to prevent host immune response and rejection [4,5]. As such, a one-size fits all cell therapy products cannot be mass produced in the traditional sense as the end-product will need to be customised for each patient. One way in which economies of scale could still be achieved for individualised cell therapy products is through a mass customisation platform. Mass customisation is a manufacturing technique that combines the flexibility and personalisation of custom-made products that best meet individual customers' needs with the low unit costs and efficiency associated with mass production [6]. It aims to achieve economies of scale through scope of products offered where per unit costs are distributed over a greater revenue base and minimised by standardising modular components and processes.

Mass customisation is not a new phenomenon but is increasingly becoming the norm as companies responds to consumer needs for individualised products. Examples of mass customised built-to-order products can be seen in a variety of everyday items such as cars, shoes, tailor-made suits, prescription glasses, bicycles, and personal computers. Perhaps one of the best- and little-known example of mass customised product is personalised business cards. Business cards used to be a premium product that were largely limited to large corporations with a healthy overhead because of the high cost of setting up print jobs. Cimpress, the parent company of its better-known brand, Vistaprint, sought to challenge conventional wisdom that printing is mostly a commodity business that one can only won with scale and customer service. They developed a mass customization platform to scale-out production through its patented aggregated printing technology and made it possible for small businesses to

have short stacks of affordable uniquely branded business cards. A business card is similar to a cell therapy product in that it also needs to be personalised with a visual identity package and design that is unique to the individual. While business cards do not have the same level of complexity as personalised cell therapy, the way the former is mass customised in large scale could provide insight into how such a platform for cell therapy could work in practice. Here, we compared Vistaprint's mass customization strategy as a real-life example to illustrate how some of the key concepts in platform design work in practice and discuss how patient-specific cell therapy products could be produced using a similar approach.

MARKET OF ONE

Before the 1990s, getting a business card was an expensive and lengthy process mostly limited to larger corporations and businesses who could afford it. It involved going to a brick- and-mortar print shop, talking to a sales rep in person, discussing order requirements, getting a design from either a pre-made template or through a graphic designer, then personalised with name, logo and a set of branding colours. Once a design was finalised, a physical template was made by laying multiple copies of the design across a large sheet. This template was then used for large scale production via printing press (Figure 1a). Because there was a huge amount of fixed costs associated with the initial production set-up - it cost as much to print 150,000 business cards as to print 1,000. Small businesses wanting small volumes were often left to pay the hefty price or resort to their own solutions.

Recognising the underserved segment of the market, Vistaprint sought out to target those low-end "micro-businesses" that were attempting to desktop-publish their own brochures and business cards at home. To reduce the high initial set-up cost, Vistaprint focused on scaling out the process: increasing the number of individual orders in one set-up and running them all in parallel to split the costs. Although this seems simple enough, it's not so straightforward as there are multiple points along the manufacturing process that could be scaled out. For example, each job could be set up to use multiple printers running concurrently. Or, multiple orders could be processed using just one printer. In Vistaprint's case, instead of setting up the physical template with copies of a single order, they laid out multiple individual orders across a single sheet as if it were one run, print to a thousand sheets deep, then cut vertically and separate them into stacks of individual orders (Figure 1b). This allows them to serve 150 customers with a 1000 business cards in one job instead of 150,000 business cards for just one customer. By aggregating multiple orders into one run, they are able to split the set-up cost across to reduce the overall price [7].

The current workflow for the biomanufacturing of autologous cell therapy products resembles the early days of business card production from local brick-and-mortar print shops in many ways. Patients must visit a regional cell procurement and infusion clinic in person for their cells to be harvested. Desired cell types need to be separated or enriched from the rest of the sample through aphaeresis, then sent to a centralised cell manufacturing facility where they will be cultured, modified, and expanded into clinically relevant quantities (Figure 2a). Between initial collection of raw material and final administration of a product, dozens of hand-off points and processes take place. Much like setting up a classic print job, biomanufacturing gene and cell therapy is associated with a huge set up cost - whether the cells are destined to treat one patient or expanded to treat 50 patients, the set-up cost is fixed. Similar to Vistaprint's approach, one way to reduce the initial set-up cost is to scale-out the process and run multiple orders in parallel to split the cost. But scaling out by simply replicating what is performed with a single unit does not permit a product to be mass customised; neither will this lead to effective cost reduction.

Indeed, the success of Vistaprint is not just based on its aggregated printing method but hinged upon several factors quintessential to building a mass customisation platform. These include: 1) standardisation and modularisation of sub-components and processes, 2) front-end service platform for high throughput order elicitation, and 3) automated job scheduling, production planning, supply-chain management via computer integrated manufacturing.

STANDARDISATION AND MODULARISATION OF COMPONENTS AND PROCESSES

A key component to Vistaprint's mass customisation platform is in its design software. Vistaprint built a web-based platform packaged with an extensive library of pre-designed templates, where customers can browse, choose, and customise. The software not only allows consumers to become an integral part of the design process, it also set the design boundaries by limiting options to only the tools and templates provided [7]. By requiring that all designs to have the same physical attributes, this allows individual orders to be laid out consistently and evenly across the template, which minimised the number of variables that needs to be optimised; this effectively standardised part of the manufacturing process.

Standardisation is one of the critical enablers of mass customisation. Products built on a common standardised platform can be customised by mixing-and-matching different components to achieve product variety or product personalization. Swaminathan outlined four standardisation approaches to mitigate the negative effects of increased product variety and variability: parts standardisation, process standardisation, product standardisation and procurement standardization [8]. Here we discuss the first three approaches, which are applicable to cell therapy.

Parts standardisation is the most widely adopted approach in mass customisation. It uses common components or subsystems across members of a product family, which reduces costs, inventories, and parts proliferation. This allows economies of scale to be achieved by mass production of standardized parts, risks to be reduced through pooling of common components, and predictability of components to be enhanced by limited parts [8]. For cell therapy, "parts" can be regarded as any components that goes into the assembly or manufacturing of the final product. These include culturing media, biomaterials, bioreactor vessels, chemical reagent, DNA vectors, cell types, donor material etc.

Process standardisation is typically based on sharing of a common process either at the beginning or towards the end of the

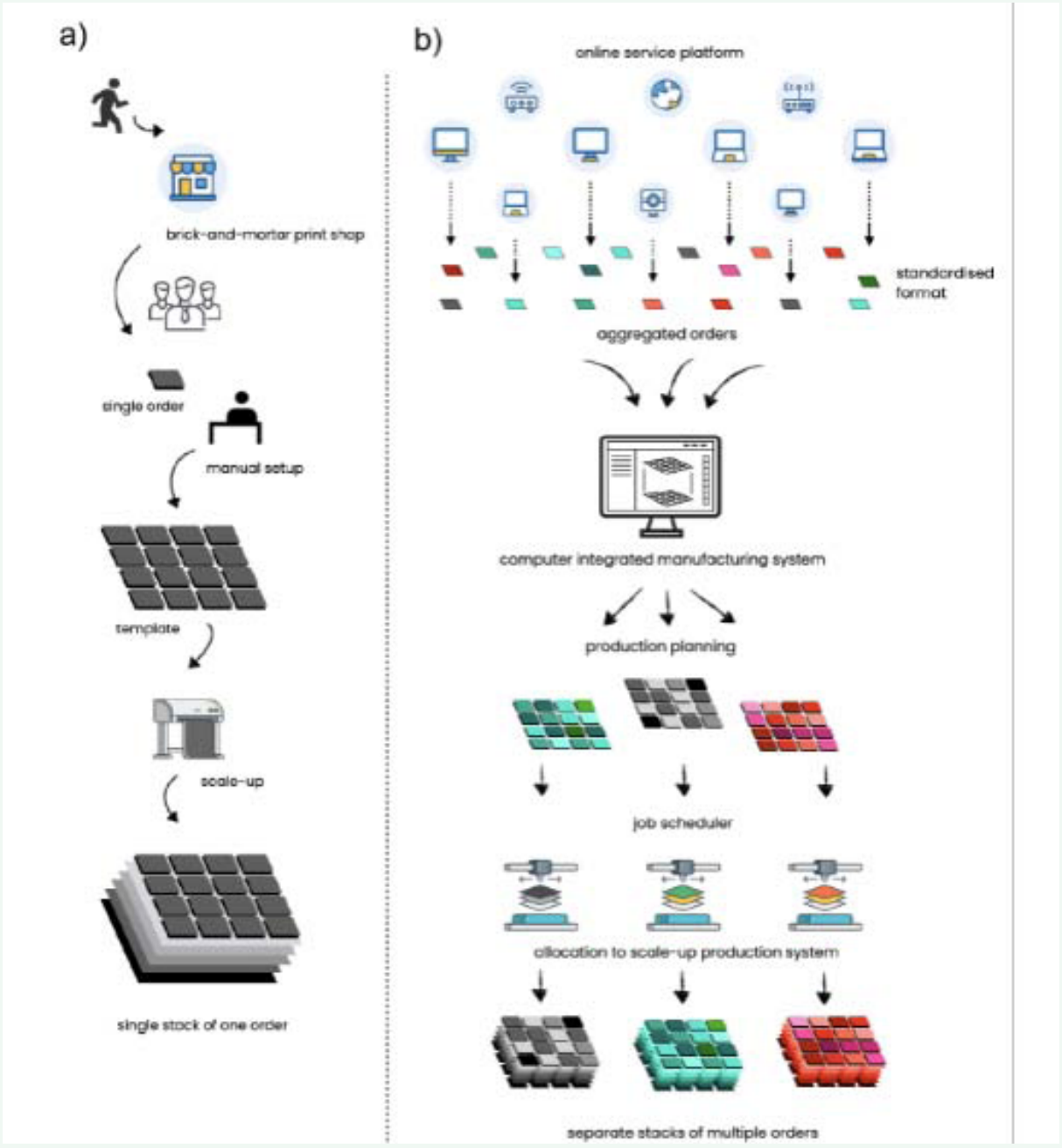

Figure 1 Schematics of printing production workflow in traditional brick-and-mortar shop, and Vistaprint's aggregated printing technology. a) In traditional printing production, customers have to physically go down to the shop to get a business card design. This is then passed down to pre-production where a physical template is made by duplicating multiple copies of the order across a sheet. Scale-up is achieved by printing multiple copies of the template through a roller press, which result in a large stack of a single order. b) in Vistaprint's aggregate model, customers browse through a library of business card designs and place order directly online. Production is scaled out by aggregating online orders via a computer integrated manufacturing system, which automatically sorts, and plans production based on similar design attributes. Sorted jobs are then dispatched to the appropriate printer in the production network, resulting in multiple stacks of individual orders.

manufacturing process. For engineered cell therapy products, this could be at the aphaeresis stage using standardised procedure, at the genetic manipulation stage using standardised transduction protocol, or at the expansion stage using standardised manufacturing practices. Delayed product differentiation (or form postponement) is when the standardisation is at the front end of the processes; customisation or differentiation steps are delayed or postponed until as late in the process as possible [9]. This enables the firm to store inventory in semi-finished form and later customise the product according to requirements. The derivation and expansion of pluripotent stem cells (PSCs), could be an example of front-end process standardisation; subsequent differentiation of PSCs into the different tissue lineages could then be delayed until order fulfilment (Figure 2b). Alternatively,

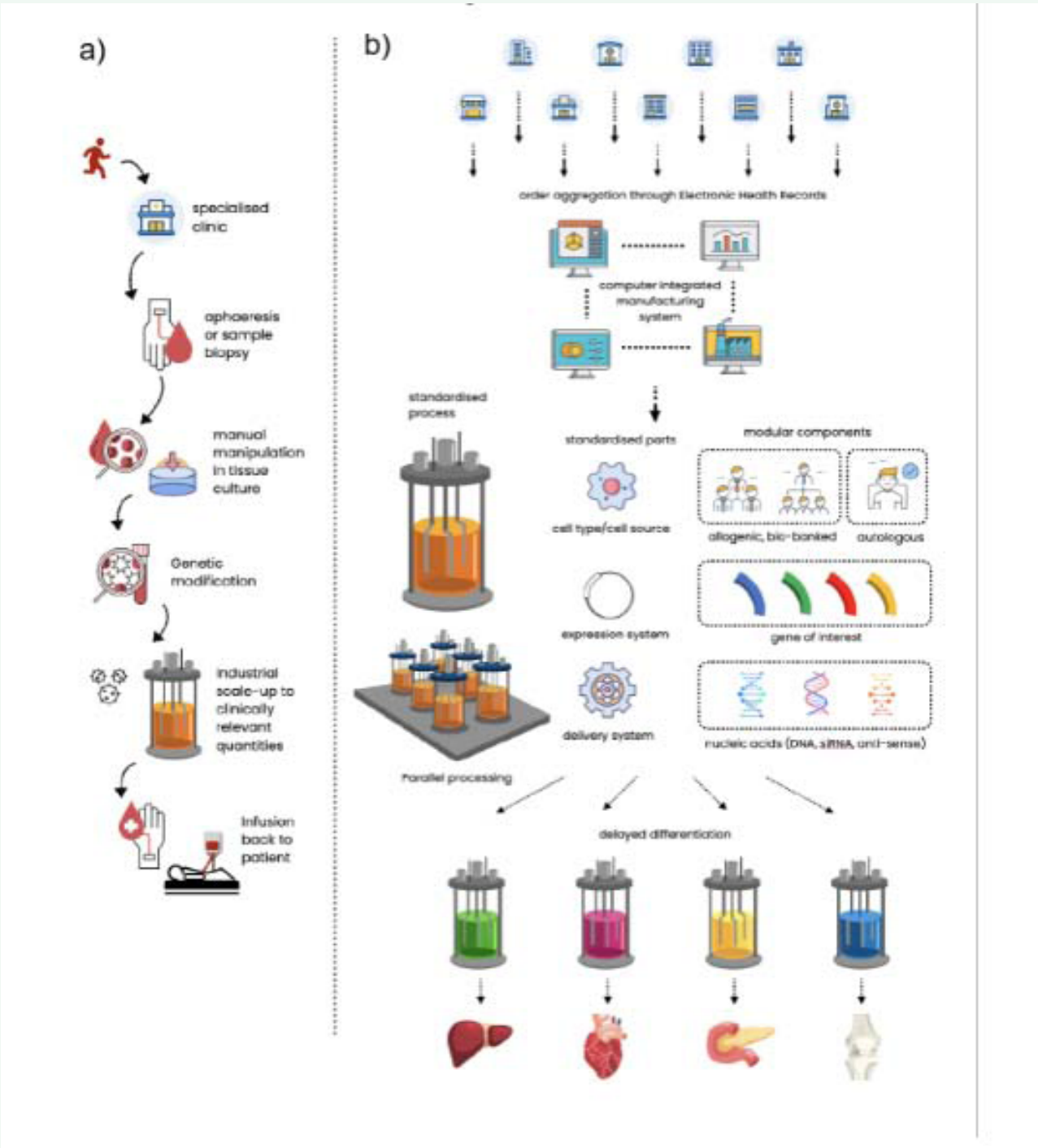

Figure 2 Schematics of current biomanufacturing workflow for autologous cell therapy products and the proposed mass customization platform. a) In current biomanufacturing workflow, each individual order is sent to a production facility where patient's cells are manually manipulated in tissue culture and genetically engineered to impart the therapeutic property. The modified cell is then passed onto a manufacturing facility where scale-up is achieved by expansion in a bioreactor. b) In a mass customization platform, orders are aggregated from multiple treatment centres simultaneously via Electronic Health Records. Production is scaled out by aggregating orders via a computer integrated manufacturing system, which sort orders based on similar specification, genomic profile etc.., then dispatched to the appropriate manufacturing platform within the production network. Economy of scale is achieved at the component level by mass production of standardizing components (e.g. expression system, delivery system). Product variety or product personalization is achieved by mixing and matching modularized components (e.g. gene of interest, type of nucleic acid molecule). Cells are either sourced directly from the patient (autologous) or from a biobank of HLA-matched donor materials (allogenic). A standardized process is applied to expand large quantities of PSCs as semi-finished product, then subsequently differentiated into tissue-specific lineages just prior to order fulfilment.

a single minimally manipulated allogenic product could be mass produced using standardised processes, then personalized at the end to optimise immune compatibility to the patient.

In product standardisation, a firm offers a wide range of end products, but, using the 80/20 rule, stocks only a few of them in the inventory. The advertised availability of products is thus far greater than actual availability on average [8]. This is not a true mass customisation strategy per se, but one approach to offer a large range of near-personalised product without the runaway cost of a large inventory. The applicability of this approach to cell therapy may be limited to minimally manipulated products such as cord blood, bone marrow, hematopoietic progenitor cells, or biobanks offering HLA-matched induced pluripotent stem cell (iPSC) lines, such as CiRA's at Kyoto University [10].

Closely linked to the discussion of standardisation is modularisation. Modularisation is an approach for organising complex products and processes by deconstructing them into simpler portions so they can be managed independently and yet operates together as a whole [11]. Modular approach is an additive design strategy wherein product distinctiveness and personlization can be appropriately achieved by combining different standard modules [12]. A "module" can be regarding as a self-contained, distinct, and identifiable unit that serves as a building block for an overall structure [8,13]. For part standardisation of engineered cell therapy products, a module can be regarded as the gene delivery system, which is modularised by the gene of interest, by the choice of expression system, or by the types of nucleic acid molecules (Figure 2b). Similarly, for process standardisation, the modular process could be the differentiation of PSCs into tissue lineages using a standardised approach, modularized with different media components.

The challenge with cell therapy is that consideration for which part or process to standardise extend beyond just cost effectiveness, quality assurance or product availability. Cell therapy also needs to factor in the clinical picture, such as the disease in question, the target tissue type, how well the graft can be tolerated, and the patient's existing co-morbidity should rejection need to be managed. For example, standardising the starting material using off-the-shelf allogenic tissues may increase consistency and reliability in manufacturing. But this may be more feasible for less immunogenic target tissue (e.g. liver [5], or immunoprivileged cell types (e.g. mesenchymal stem cells [14], where graft can be better tolerated. But for highly immunogenic target organs (i.e. hearts, lungs, and intestines [5], additional genetic modifications needed to evade the immune detection might end up costing more than using an autologous cell source to begin with. In short, the considerations for which part or process to standardise should be viewed in terms of the cost-effectiveness of the entire spectrum of care, in addition to the end therapeutic goal.

SERVICE PLATFORM FOR ORDER ELICITATION AND DIGITISATION

In order to achieve economies of scale through a scale-out model, a large volume of orders is needed at one time to initiate jobs. Getting sufficient quantities of orders was a challenge in the traditional brick-and-mortar print shop business model, which have a small network of clientele that required in person visits for order placement. This type of service platform tended to have a relatively fixed and small volume of orders. One of the key technology developments that enabled Vistaprint to scale-out and implement the mass customisation platform was the introduction of the World Wide Web. When Vistaprint started out in 1994-1995, people were beginning to get connected to the internet at an accelerated rated. Vistaprint capitalized on this boom and built a web-based service platform that allowed customers to place orders directly online. An online platform unrestricted the geographical limitation typically faced by local brick-and-mortar shops, streamlined the order placement process, and enabled an enormous number of orders to be collected from across the country simultaneously [15]. The web-based software also provided an interface for self-service, which effectively digitised information from the mind of the customer to the point of production [16]. This not only eliminated the lengthy and costly manual steps of working with sales reps and designers, but also allowed orders to be handled by a computer integrated manufacturing system.

Similar to the printing industry, orders for cell therapy products could come from the treating team based at a hospital or clinic that services a fixed geographical region. To increase the throughput of order aggregation, a web-based centralised service platform may provide a more efficient way to collect orders from multiple treatment centres. The challenge, however, is how to implement such a service platform. Because cell therapy products are personalised living tissues, a detailed pre-treatment work-up involving a battery of lab tests, genetic analysis and pathology reports may also be required at the time of order. Many of the required details are currently generated by clinical resources captured on paper or multiple media, across a variety of information systems and networks, which required additional manual input to coordinate. As well, the acquisition of starting material, manufacturing, and transport of the cell therapy products needs to be aligned with the scheduling and availability of the patients, their physicians, and the treating team. Thus, a web-based platform for cell therapy not only needs to provide a self-service function for order elicitation, but also harmonise and coordinate the flow of information between the health care providers, manufacturers, supplier, and patients.

One way in which order elicitation and digitisation of patient info could be achieved is through Electronic Health Records (EHR). EHRs are real-time, patient-centred, digital records of health information and clinical care generated and maintained by healthcare providers in standard clinical care settings [17]. This information includes demographics, medical and surgical history, allergies, medications, diagnoses, procedures, details from patient encounters, as well as results and reports from various clinical studies, which are information that may be critical to the manufacturing of autologous cell therapy products. EHRs also track practice-management functions such as scheduling, billing, and insurance information [17], which could include aphaeresis, operating room harvesting data, and infusion appointments as add-on modules. The system also enables health providers to order lab tests and prescribe medications digitally, which could be expanded to cell-based therapies as products become available, allowing orders to be submitted centrally and

simultaneously across multiple health services.

The utility of EHR extends beyond just a point-of-care service platform. The integration of genomic information into EHR are bringing personalised and precision medicine into light, which could potentially be harnessed to address the issue of product variability between different patient sample. EHR-based programs with embedded genomic test results are already being combined with clinical decision support to provide point-of-care guidance for patient- to-patient variability in drug response [18]. The use of genomic information to predict drug response, or pharmacogenomics (PGx), is a prime example of how EHR is driving personalised medicine research and implementation. Genetic variants can alter drug's pharmacodynamics, such as drug's distribution, absorption, metabolism or elimination. PGx has helped identify genetic variants, predict drug responders from non-responders, avoid adverse events, and optimize drug dose, thereby avoid adverse events [18,19]. Similarly, the use of -omics data has helped predict cell proliferation and response under culture environment. For example, comparative analysis of transcriptomic data between high and low producing clones assisted in identify chromosomal regions or genes correlating with cell productivity [20]. Further, genomics, transcriptomics, proteomics and metabolomics are already being applied to enhance protein production in CHO cell factories [21]. As such, patient-specific genomics data could be collated at the time of order acquisition and assist computer integrated manufacturing software in applying appropriate adaptive modules to compensate for patient-to-patient yield variability.

COMPUTER INTEGRATED MANUFACTURING

A web-based centralised front-end service platform for order elicitation can only be effective if the back-end order fulfilment process is supported by an efficient job handler. A computer integrated manufacturing (CIM), system is one such example of an automated job handler designed to coordinate cross-organisational production processes. CIM utilises centralised software platform to enable efficient materials handling and management while delivering direct control and monitoring of all operations, connecting what happens on the shop floor at the enterprise level [22]. It uses computers and communication networks to automate functions such as order analysis, cost accounting, design, distribution, inventory control, job scheduling, production planning, and supply chain management in a series of interconnected systems.

To illustrate this concept, we again look at the Vistaprint as an example. At the core of Vistaprint's computer integrated manufacturing platform is a job scheduler that automates the flow of information between all the orders, manufacturing systems, and suppliers. It automatically handles, coordinates, schedules, plans, and routes jobs to the production system that is most appropriate and cost effective for the type of product ordered [15]. That is, the system searches pending individual print jobs, selects those with similar printing parameters for combination into a single aggregate job, and calculates the optimal allocation of print order to optimise print quality, production costs, and timely delivery [15]. For example, when orders are received, the system starts organising them based on design pattern, ink coverage, colour usage, colour distribution, and paper type, which are meta-data embedded into each order. Orders with only black ink are grouped together into one job and sent to a monochrome printer, which is cheaper to run, while orders with 2 or 3 of the same colours are sent to the appropriately optimised colour printers (Figure 1b). The planner also makes sure that order arrangement for complex design with heavy ink usage and simple designs with light ink coverage are balanced and evenly distributed so that production artefact such as ink pooling, bleeding, blotching, dripping, and smearing are minimised. While the specifics of these production planning methods require a great deal of experimentation initially, the later adoption of CIM to automate the individual steps was critical in enabling large volume of order to be processed efficiently.

Likewise, the development of a mass customisation platform for gene and cell therapy products will necessitate some form of CIM to handle the large throughput of orders. Beyond automation of individual processes, CIM would be critical to coordinate orders, binning them based on similar biological parameters, and allocate jobs to the appropriate manufacturing platform within the production network. With sufficient large number of orders, patient-to-patient variability can be minimised by combining donor source materials with similar bio-physiological profile using empirically determined proxy for culture variability (such as biomarker status and genomic profile) into a single aggregate job such that the same compensatory culturing conditions could be applied in one batch to maintain quality, consistency, efficacy and yield. In order to enable the automation of production planning and job scheduling in this setting, biological characteristics of the product and patient-specific clinical data would need to be digitally embedded into each order so that the computer algorithm can read, sort and route the orders. The EHR mentioned in the previous section is critical for realising the potential of CIM as the "meta-data" can be submitted together at the time of order acquisition.

DISCUSSION

In this perspective article, we have presented a conceptual framework of how a mass customisation platform can be envisioned to increase the accessibility and affordability of personalized gene and cell therapy products. By modularizing and standardizing components and processes, economies of scale can be achieved at the component level, while product variety or product personalization can be achieved by mix-n-match modular components. By using an EHR as a web-based service platform, high throughput of orders and their accompanying patient-specific data can be efficiently collected at the point-of-care to enable scaling out of production. By implementing a computer integrated manufacturing platform, aggregated orders can be analysed, sorted and routed to the appropriate manufacturing systems in the production network.

While a mass customisation of gene and cell therapy would be best achieved through a centralised platform, this does not necessary mean that productions must occur at a centralised facility using off-the-shelf universal donor material. Ultimately, the real value underpinning a mass customisation platform is in the coordination of mass amounts of information. By aggregating orders systematically into a larger data set, trends, patterns, and relationships can be identified so that common

components can be mass produced or synchronised to minimise duplicated or one-off efforts (which tend to be the major driver of cost in an otherwise fragmented, uncoordinated system). Customisable options can then be maximised by scaling out to achieve economies of scope where unit costs are distributed across orders. As such, scalability is not a linear concept limited to the choice of starting material (i.e. scale-out for autologous vs scale-up for allogenic), but should be viewed non-linearly in a modular sense where economies of scale are achieved at tiered component level.

The large number of orders needed for mass customisation platform to be feasible beg the question: is there enough product varieties and patient demand at this point to warrant a mass customisation platform for gene and cell therapy products? The answer may be best addressed by considering how technologies evolve. Clayton Christensen, a professor at the Harvard Business School, who developed the theory of "disruptive innovation", said that true disruption takes place when a company conceives a product or services that supplies unserved or under-served markets, working its way up the chain, pushing formerly dominant players into shrinking high-margin enclaves [23]. In that regard, Vistaprint did not start out by offering large corporations cheaper business cards. They went to the bottom of the barrel of customers - the ones that traditional print shop could not serve - the dog walkers, tennis instructors, and the independent plumbers - and offered them a better alternative. Perhaps a better question to ask for gene and cell therapy is: who else needs clinically relevant quantities of cell therapy products for their studies? Are they scaling up production on their own using in-house facilities and equipment? What are the alternatives? Could early-phase clinical trials and drug discovery research potentially be the underserved portion of the market?

The question of when and where to start will ultimately involve iterative cycles of experimentation as the manufacturing technologies and the EHR platform continue to evolve as well. But one thing to note is that Vistaprint did not start out as a printing company. It did not develop new printers, better paper or innovative ink – Vistaprint is a software company specialising in mass customisation, which happened to find an application in printing. Perhaps the best place to start is to identify and coordinate the underserved portion of the gene and cell therapy market, which may end up revealing unmet need for a new technology that will transform the industry.

CONCLUDING REMARKS

Gene and cell therapy are being hailed as the third pillar of modern medicine [24]. Current cost of goods, however, prohibits the widespread utility and adoption of this new technology, which can delay or even hamper its further development. From the distributive justice perspective, ensuring equal and fair access to cell therapy is a duty shared by all in the research community. As such, a collaborative effort between biomedical research, process engineering, clinical sciences, and information technology would be key to realizing the full potential of cell therapy. Only through the harmonisation of interdisciplinary efforts will a mass customisation platform for gene and cell therapy be possible for personalised cell therapies.

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AUTHOR CONTRIBUTION

Conceptualization, C.Y.M.H.; Writing – Original Draft, C.Y.M.H.; Writing – Review & Editing, C.Y.M.H., D.E.R.

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