PART IV
EXPERT'S REPORT

Statement

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Hemogenyx Expert Report

Aruwon Ltd is an independent consultancy providing expertise and analysis to companies and institutions active in the life science sector, including support on M&A, licensing and business strategy.

Aruwon Ltd has been instructed by the management/board of Hemogenyx Pharmaceuticals Limited ("HPL"), parent company of Hemogenyx LLC ("Hemogenyx") to provide an independent technical and commercial analysis of the company and its product pipeline, including assessment of the background, addressable markets and competition, as well as the associated risks.

This analysis will form part of the listing document associated with the merger of HPL with Silver Falcon plc and the proposed listing of the merged entity on the London Stock Exchange.

This report has been prepared with due diligence based on the information provided by Hemogenyx or obtained from public domain sources deemed reliable by Aruwon. While every effort has been made to ensure the accuracy and completeness of the information and data presented, Aruwon cannot accept liability for errors or omissions. In particular, the industry areas under examination are fast moving and any change in circumstances may render some or all of the information or conclusions incomplete, obsolete or invalid.

It should be noted that this report does not seek to provide any guidance as to the validity or otherwise of any intellectual property filed, held, or licensed by Hemogenyx.

Aruwon is not acting as an investment advisor. This report is specifically limited to the matters set out above and is not to be taken as giving any advice on the merits of an investment in Hemogenyx.

Christopher Redhead

Managing Director, Aruwon Ltd

Summary

Hemogenyx is a private company based in Brooklyn, NY, USA focussed on developing new treatments for blood diseases, such as leukemia, lymphoma and bone marrow ("BM") failure based on blood stem cell (bone marrow/hematopoietic cell) transplantation. The company has developed two potentially complementary technologies which it believes will make this frequently life-saving procedure available to both a much greater number and a far broader range of patients than is currently possible.

Previously used as a last resort, Hematopoietic Stem Cell Transplantation (HSCT) is now the fastest growing procedure in the US, used in an increasing range of blood cancers and other non-malignant disorders. Most patients receiving HSCT must first receive conditioning to prepare them for transplant; currently a harsh process unsuitable for the old or less healthy. Hemogenyx has developed a gentler antibody-targeted approach that will open the procedure to more vulnerable patients. With the increasing use of HSCT, access to appropriate donors is an increasing problem with many patients unable to find a match. Hemogenyx's second technology uses a special class of cells that it has identified and can isolate from donors or the patients themselves. These cells can generate cancer-free, patient-matched blood stem cells, which can then be used in HSCT. This the company believes will improve the efficacy of BM/HSC transplants and make BM/HSC transplants a viable treatment option for many patients who wouldn't otherwise be able to find a matching donor.

The Company has already established sound proof-of-principle for both the conditioning and the transplant cell technology through studies conducted in well-documented models of the human hematopoietic system in animals. Studies demonstrate that the Hemogenyx antibody-targeted conditioning regimen is efficient and well tolerated, providing a good environment for subsequent stem cell transplantation. Studies in similar animal models indicate that the newly discovered class of blood stem cells are capable of safe and efficient restoration of the human hematopoietic system. The cells are amenable to routine isolation and frozen storage and thus routine clinical use. Both technologies are complementary with and would significantly enhance current clinical practice. As such, they have potential as a substantial driver in the growth and application of HSCT.

The company must now reproduce these results in human clinical trials. The focus will be on orphan indications where there are limited therapeutic alternatives. This approach is designed to facilitate both trial approval, patient recruitment as well as smooth the regulatory path.

The impact of potential competition is difficult to measure given the number of years before expected market entry. Cell therapy and immunotherapy are rapidly evolving areas and true comparisons can only be made in the light of clinical outcomes. However, the technologies promise considerable advantages over the existing technologies. If successful, the Hemogenyx technology has the potential to take a substantial share of a rapidly growing market already valued at $3-$4 billion based on pricing information from the Center for International Blood and Marrow Transplant Research (CIBMTR) and other sources.

The company has a strong management team that combines scientific excellence with expertise in clinical and commercial development.

While, given the opportunity and encouraging progress to date, the prospects for both programmes look bright, the relatively early stage of both means the risks are also high. Success in the human trials is clearly critical.

Bone marrow and Human Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) includes a number of procedures whereby the blood forming stem cells of a patient are depleted and then replaced by infusion of hematopoietic stem/progenitor cells derived from the patient him/herself (Autologous HSCT) or from a donor (Allogenic HSCT). HSCT was historically performed on patients as a last resort where other treatment options had been exhausted. However, it is increasingly used for curing a range of haematological malignancies, repairing dysfunctional blood stem cells (Negrin, 2014) and inducing tolerance to solid organ transplants. Over the last forty years more than 1M patients have undergone HSCT and it has now become a highly valuable medical procedure in the US with 21,169 HSCTs performed in 2014.

There remains some debate over the relative benefits of autologous over allogeneic HSCT. Transplant-related deaths tend to be lower in autologous transplants due to the lack of graft-versus-host disease (GVHD) and the lower incidence of infection resulting from the quicker re-establishment of cells responsible for the immune response. Remission through the carry-over of tumour cells, however, is a clear risk with autologous HSCT. Nonetheless, analysis of the data from the Health Resources Services Administration (HRSA) reveals that in general autologous HSCT is favoured for treatment of both haematological and in solid tumours.

Figure 1 2013 Data From The Health Recourse And Service Administration (HRSA) Showing Transplant Activity By Disease Category And Cell Source.

Year Disease Category	Allogeneic (Related and Unrelated)			Autologous				Grand Total
	Bone Marrow	Cord Blood	Peripheral Blood	Bone Marrow	Cord Blood	Peripheral Blood	Data not available	
2013	1,835	836	5,677	15	2	10,854	1	19,220
Acute lymphoblastic leukemia (ALL)	301	147	665	0	0	17	0	1,130
Acute myelogenous leukemia (AML)	457	317	2,214	1	0	59	0	3,048
Autoimmune Disease	5	1	4	0	0	13	0	23
Chronic myeloid leukemia (CML)	65	27	175	0	0	0	0	267
Disorders of the immune system	114	42	40	2	0	0	0	198
Histiocytic disease	51	10	12	0	0	2	0	75
Hodgkin lymphoma	38	21	168	1	0	824	0	1,052
Inherited abnormalities of erythrocyte function	155	37	48	0	0	2	0	242
Inherited disorders of metabolism	22	42	6	0	0	1	0	71
Inherited platelet abnormalities	3	4	0	0	0	0	0	7
Multiple myeloma/ plasma cell disease	9	3	171	4	1	6,311	1	6,500
Myelodysplastic/myeloproliferative	191	77	1,066	0	0	3	0	1,337
Non Hodgkin lymphoma	106	65	719	3	0	2,656	0	3,549
Other acute leukemia	30	12	57	0	0	2	0	101
Other leukemia	27	15	256	0	0	11	0	309
Severe Aplastic Anaemia	246	13	58	0	1	1	0	319
Solid tumors	2	1	10	4	0	939	0	956
Other disease	13	2	8	0	0	13	0	36
Grand Total	8,002	4,268	25,498	147	13	48,573	1,562	88,063

http://bloodcell.transplant.hrsa.gov/research/transplant_data/transplant_activity_report/bydiseasecategorycellsource.pdf

Both autologous and allogeneic HSCT require two essential steps. The first involves a conditioning step which entails sufficient ablation of the patient's HSC and their immune system. The second step involves the infusion of the autologous or allogeneic HSC.

Conditioning

Conditioning is an essential component of HSCT and has been extensively reviewed (Gyurkocza & Sandmaier, 2014). Designed to reduce both the probability of the rejection of the grafted cells and the disease burden, it involves the ablation of the patient's HSC and immune system. Historically consisting of the use of supra-lethal doses of radiation and chemotherapeutic agents, the harshness of the procedure limited the HSCT to younger 'fitter' patients. However, the realisation of the significant benefits of Graft versus Tumour (GvT) reactions against malignant cells and the subsequent introduction of reduced intensity and non-myeloablative regimens has resulted in HSCT being increasingly used on older and more medically infirm patients. The conditioning regimens may therefore be divided into three groups high dose, reduced intensity conditioning and non-myeloablative conditioning.

High Dose

Myeloablative, or "high-dose" regimens, consisting of alkylating agents (single or multiple) with or without TBI (total body irradiation), are expected to ablate marrow hematopoiesis, not allowing autologous hematologic recovery. TBI is associated with considerable short and long term side-effects and so is frequently replaced with other chemotherapeutic agents.

Reduced Intensity and non-myeloablative conditioning

Observations from the use of HSCT over the last thirty years have increasingly indicated that relapse was significantly reduced in patients who developed GvT, indicating that GvT plays a significant role in clearance of malignant cells in the host. This was also borne out in studies that indicated that patients receiving unmodified grafts enjoyed lower relapse rates than patients receiving syngeneic or T-Cell depleted grafts. This has led to the development of less harsh reduced intensity conditioning (RIC) and non-myeloablative conditioning (NMC), which not only reduced the relapse into malignancy, but also opened the door to the use of HSCT in older or more infirm patients. These RIC regimens cover a spectrum of intensities (Figure 2) that allow the adaptation of the conditioning to suit the individual patient or disease.

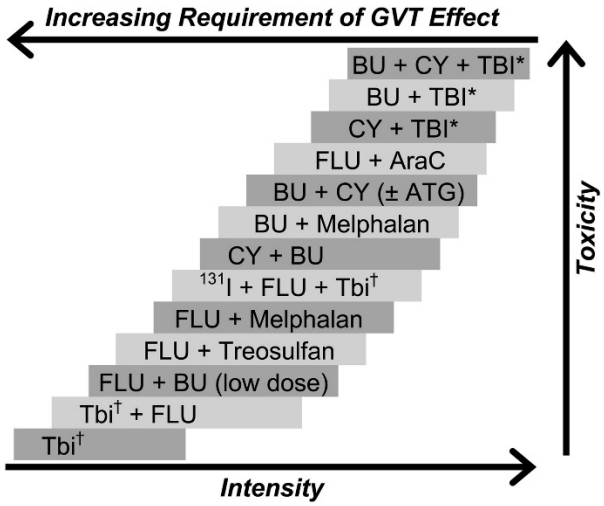

Figure 2 GvT and RIC (Gyurkocza & Sandmaier, 2014)

Antibody-targeted conditioning

The success of RIC regimens has led to the development of antibody-based regimens that target tumour cell lineages or T-cells. Given the sensitivity of leukaemias and lymphomas to radiation, antibodies targeted at a number of hematopoietic cell-specific antigens, including CD20, CD33 and CD45 have been labelled with radioisotopes to deliver a radioactive dose.

A number of radiolabelled antibody approaches have been used and shown to provide conditioning. Bexxar (^{131}I-labelled tositumomab), which targets the CD20 receptor, has been used with some success for the preconditioning of Non-Hodgkin Lymphoma patients (Krishnan, Nademanee, & Fung, 2008). Encouraging results for conditioning have also been reported for Zevalin (^{90}Y-ibritumomab) (Shimoni, Zwas, & Oksman , 2007), also anti-CD20. CD20 is specific to B-cells and thus is probably better suited to the treatment of B-cell cancers than general conditioning. As a result, neither is in widespread use for conditioning.

A further ^{131}I antibody targeting the CD45 receptor, Actinium Pharmaceuticals' Iomab-B, commenced a phase 3 trial in H1 2016 for conditioning in relapsed AML. CD45 is fairly ubiquitously expressed across the blood system, and Iomab-B will provide generalised irradiation of hematopoietic cells. Iomab-B used before autologous or allogeneic HSCT has shown encouraging results in elderly patients with advanced AML or MDS (Pagel, Gooley, & Rajendran, 2009).

The development of the RIC regimens has meant that there has been a significant increase in the number of patients, particularly elderly patients, who are suitable for HSCT (Figure 3).

- *Figure 3 Progressive increase in HSCT in older patients*

Stem cell infusion and donor selection

Once the patient has been conditioned, new stem cells will be infused. The choice of the donor will largely depend on the patient's indication and individual circumstances. Autologous cells are sourced before treatment most commonly from the patient's own peripheral blood, but also from bone marrow. The choice of source of allogeneic cells is more complex depending not only on the condition of the patient, but also the availability of the relevant donors.

Donors are matched according to their HLA (Human Leucocyte Antigen) genotyping, now most commonly performed by molecular typing (Eng & Leffell, 2011). The degree of HLA matching is critical to long term patient survival. Potential donors may be divided into three groups fully matched, haplo-identical (at least 50% match) and mismatched. Fully matched may most easily be obtained from a twin, but can also be found amongst other siblings, as well as individuals within the broader population. The ideal donor is generally a fully matched sibling. If this is unavailable, an unrelated fully matched donor is sought. As this can take time, in cases of urgency the clinician may opt for an infusion of Umbilical Cord Blood (UCB) or a haploidentical donor.

UCB as a source

Collected at the time of delivery, UCB is seen as an increasingly useful source of HSC. Stored frozen and ready typed in blood banks, unrelated UCB can provide a rapidly accessible source for HSCT, when an HLA matched donor cannot be identified in the right time frame. Its advantages include:

Expanded donor pool – increased representation of ethnic minorities in the unrelated UCB banks and more effective use of partially HLA-matched donors (Querol, Rubinstein, & Marsh, 2009).

Ease of procurement and lack of donor attrition – tested prior to storage for infections, blood and HLA-type, and cell dose, (Gluckman, Rocha, & Chevret, 2001), avoids the risk of donor attrition and speeds access.

Graft-versus-host disease (GVHD) –incidence and severity of acute and chronic GVHD among unrelated UCB recipients is lower than reported with matched unrelated donor marrow or partially-matched family member marrow allograft (Rocha, Wagner, & Sobocinski, 2000).

Safety for donors and recipients – easily and safely collected after delivery with reduced risk of carrying infection

The limitations of UCB largely stem from the relatively low abundance of stem cells, which frequently leads to reduced rates of engraftment, leading to graft failure, and delayed reconstitution of the immune system, leaving the patients vulnerable to infection. While these limitations can be mitigated by the use of double transplants or ex-vivo expansion, there is a pressing need to increase the efficiency of UCB for HSCT.

Hemogenyx Technology and Approach

Our review indicates that while there have been considerable improvements in both conditioning and the availability of donor tissue, there remains a substantial number of patients for whom existing regimens are too harsh or who cannot identify an appropriate donor. Hemogenyx has developed two technologies with which it believes it could both broaden the use, as well as increase the safety of HSCT. The first is aimed at improved conditioning opening up HSCT to an even broader set of patients. The second is aimed at developing a new source of human hematopoietic stem/progenitor cells for use in HSCT.

Conditioning with CDX

The Hemogenyx CDX technology is designed to clear the patient's existing hematopoietic stem cells using his/her own immune system. The technology uses bispecific antibodies. These double-headed molecules combine specificity for the T-Cell receptor at one end with specificity for an as yet publicly undisclosed specific hematopoietic stem cell receptor at the other. This causes T-Cells to bind to and subsequently destroy the progenitor target cells. While yet to be tested in man, the technology has already been shown to work efficiently in an established mouse model constructed to mimic the human hematopoietic system.

Chimeric mouse studies

Hemogenyx has tested its CDX platform in immune-deficient NSG mice stably engrafted with human hematopoietic stem cells (HSC); a powerful and well documented model of the human hematopoietic system (Shultz, Lyons, & Burzenski, 2005). The tests have shown that treatment with CDX specifically targets human HSC eliminating the human compartment of the mouse blood system. The CDX approach should not only avoid the overall toxic effects generated by the use of radiation and chemotherapeutic agents used in traditional conditioning, but also any direct toxic effects on mature blood cells such as B-cells, T-cells and myeloid cells including macrophages and neutrophils.

Experiments performed by Hemogenyx have demonstrated that infusion of chimeric mice with the CDX bispecific antibody causes a dramatic decrease in the human blood cells in the chimeric mouse reverting them into their native non-chimeric state. This decrease in human cells is characterized by a relatively rapid decrease of the number of myeloid cells carrying the marker CD33 followed by a slower decrease in mature T and B cells carrying markers hCD3 or hCD19, respectively (Figure 4). This is consistent with a specific depletion of human hematopoietic stem/progenitor cells and was not accompanied by any other detectable adverse events.

*Figure 4 Treatment with CDX of humanised NSG mice produces a progressive decrease of the levels of total human hematopoietic cells (**A**) and also the levels (**B**) of T-cells (% $hCD3^+$ cells of total $hCD45^+$ cells), B-cells (% $hCD19^+$ cells of total $hCD45^+$ cells) and myeloid lineages (% $hCD33^+$ cells of total $hCD45^+$ cells) in the peripheral blood (n=27) progressively over 1, 3 and 5 weeks (right red and green data sets) compared to control levels (left black and blue data sets). The treatment was repeated in twenty-seven chimeric mice (N=27).*

Importantly for its potential role in conditioning for HSCT, preliminary experiments indicate that CDX treated mice can subsequently be again engrafted with human HSC that turns them back into chimeric humanized mice where part of their hematopoietic system is human. This emulates the conditioning of patients followed by a HSCT. While these effects have yet to be repeated in human subjects, the good efficacy and safety demonstrated in this well-established mouse model is clearly encouraging.

Hu-PHECs a new source of HSCs

As outlined in a published patent (SANDLER, 2014), Hemogenyx has been able to generate a new source of HSC using the cells that line the inside of adult blood vessels (a subset of endothelial cells). This is based on the observation that HSC arise from embryonic hemogenic endothelial cells, which appear to involve an intermediate cell type that still resides in postnatal/adult endothelia. Dr. Sandler showed that it is possible to isolate these intermediate cells and restore their hematopoietic potential. Known as Hu-PHECs (Human-Post-Natal Hematopoietic Cells), these HSCs can be generated from a range of tissues, including the umbilical cord and adult liver

Hu-PHECs

Data on the Hu-PHECs clearly show that Hu-PHECs can be generated from umbilical cord and liver endothelia. The outline details of the process are summarised in a patent application (SANDLER, 2014). As we understand it, cells are prepared from endothelia and those expressing a specific combination of markers (CD45 and CD144) can be purified in an automated fluorescent cell sorter. These cells can then be cultured on a feeder layer of a subset of embryonic liver cells, where they are able to multiply and regain their hematopoietic potential.

Studies where Hu-PHECs isolated from human umbilical cord are transplanted into the NSG mouse model have shown that these cells are capable of stable engraftment and are able to generate what appears to be a near full repertoire of human blood cells.

The company has also been able to show that Hu-PHEC cells can be generated from liver endothelia. While they have yet to generate sufficient material to perform transplantation due to insufficient access to suitable human livers, the mouse equivalent M-PHECs isolated in the same way have been shown to be capable of engraftment in these models.

While the mouse NSG model is well established and documented, it has some limitations (Brehm, Shultz, Luban, & Greiner, 2013). However, in the light of the data to date, we are optimistic that the results may be transferable to human patients.

The company has also shown that it is possible to culture and expand the Hu-PHECs for up to 11 days. This opens up the possibility that autologous liver Hu-PHECs could be expanded to help deliver the appropriate genetic material capable of correcting inherited deficiencies and/or provide treatment of disease.

Development Plan and Strategy

Although Hemogenyx has established very encouraging proof of principle for both its CDX bispecific conditioning regimen and use of Hu-PHECs for hematopoietic reconstitution in the mouse NGS model, there is considerable work to be done before either product will be ready for use in humans.

CDX Conditioning

The company has a number of milestones to meet for its lead product before it is able to initiate phase I clinical trials in 18 months. Most significantly, it will need to engage with the FDA to determine the nature and scope of pre-clinical studies required for its IND, as well as gaining orphan designation for the use of CDX for conditioning and subsequently for certain types of leukaemia.

Below is a summary of the development milestones for Hemogenyx over the next 18 months for the CDX bi-specific antibody:

- Completion of pre-IND consultation programme
- Preclinical evaluation of additional clones of CDX antibodies
- Completion of IND-enabling studies
- Submission of IND application to FDA
- Application for Orphan Drug Designation
- Completion of pre-IND consultation programme

We would anticipate a reasonably straight forward path for development. The development path for the antibody-based conditioning agent has already been at least partially mapped out through the development of several currently approved bispecific therapeutic antibodies (e.g. Blinatumomab, Amgen) and more than thirty bispecific antibodies in clinical trials (Fan, Wang, Hao, & Li, 2015).

Hu-PHEC transplantation

Hemogenyx has also outlined a number of milestones for its Hu-PHEC programme. Of these milestones, we would see the pre-IND consultation as being the most critical, as this will drive the overall speed of entry into the clinic and ultimately into the market.

Below is a summary of the development milestones for Hemogenyx over the next 18 months for the Hu-PHEC:

- Preclinical toxicological studies for Hu-PHEC Umbilical
- Pre-IND consultation with FDA in relation to Hu-PHEC Umbilical
- Collection of cells and tissue samples for transplantation in relation to Hu-PHEC Liver
- Continuing research and development for methods of expansion of Hu-PHEC
- Achievement of proof of principle of transplantation of human liver derived Hu-PHEC

- Preclinical toxicological studies for Hu-PHEC Umbilical

The key strategy to expedite the development of the Hu-PHECs will initially be to target patients who currently have no other option due to lack of appropriate matched donors or life threatening time constraints. This would include patients who develop Aplastic Anaemia. Clinical proof of principle in these 'last resort' patients will facilitate the initiation of trials in a broader patient population.

Design of the late stage pivotal trials will clearly depend on the results of these initial phase I/II trials. With these unlikely to report before year three, it is unlikely that the products will gain approval before year five.

Regulatory path

CDX

The regulatory path for CDX has at least partially been mapped out for CDX by the development of Iomab-B by Actinium Pharmaceuticals, currently in a Phase 3 clinical study for bone marrow conditioning in relapsed refractory AML. A more specifically targeted product without the complexity of a radionucleotide, we would expect that the regulatory path would be far less complex for CDX compared to Iomab-B. There are certainly a large number of relapsed patients that would not easily tolerate existing conditioning regimens. With few other options, they may provide good initial candidates for CDX clinical trials. Given the relatively small number of patients involved and the lack of alternatives, we believe it is likely that the CDX would receive Orphan Status from the FDA. This would qualify the product for accelerated development and approval under FDA rules.

Hu-PHECs

Hemogenyx has indicated that it will also seek an orphan path for its Hu-PHEC programme. The company has already achieved orphan status for the use of Hu-PHECs for patients with Aplastic Anaemia and will seek the same designation for a range of other rare genetic and/or pediatric diseases, where there are currently limited alternative options.

Competitive landscape

CDX

The major competition will be the existing conditioning regimens for HSCT (Gyurkocza & Sandmaier, 2014). There is clearly a need for an effective, but more benign conditioning regimen to enable more vulnerable patients to benefit from HSCT. While the mouse data suggest that it should have strong advantages, the extent to which a potentially higher priced CDX will displace existing regimens will clearly depend on the observed clinical benefits.

With regards to other antibody-based regimens, while the radio-immunotherapy Iomab-B from Actinium Pharmaceuticals may reach the market significantly earlier, the logistics of radio-isotopes use and the lower specificity of action may restrict its widespread adoption. A novel product positioned as a more targeted therapeutic than a more general conditioning regimen will likely have a clear advantage.

Further, Magenta Therapeutics Inc., based in the USA, is developing anti-CD45 antibodies linked to a toxin aiming for a less toxic and more effective conditioning approach to remove existing HSC and possibly tumour cells. In our opinion, Magenta's research is at a very early preclinical development stage. It may, if successful, eliminate the problems with respect to radiotherapy and decrease those associated with chemotherapy. However, it would not resolve the problems due to the lack of specificity of the anti-CD45 antibodies, which are believed to lead to non-specific and unrelated cell and tissue effects.

Magenta is also investigating the possibility of developing processes to improve HSCT procedures, although it is believed to be at the early discovery stage. Furthermore, the process as currently outlined would not overcome the problem of tissue matching. Magenta recently in-licensed an early stage clinical programme from Novartis – MGTA-456 (formerly known as HSC835, or SR-1) - as part of a $50m fund raising. MGTA-456 has demonstrated expansion of cord blood stem cells in a Phase I/II study and thus could also improve transplant outcomes.

Hu-PHECs

Competition for Hu-PHECs is difficult to assess given the relatively early stage of development and the number of years to market.

One such competitor, Nohla Therapeutics Inc., is developing a method of ex vivo expansion of hematopoietic progenitors isolated from cord blood to supplement and enhance cord blood HSCT. The main advantage of Nohla's approach is that it generates a pure population of cells that does not include donor T-cells and therefore can be used without HLA ("Human Leukocyte Antigen") matching. When used in combination with standard of care cord blood transplantation, these expanded progenitors shorten the time required for neutrophil and platelet recovery, helping reduce the risk of infection and graft failure. Nohla's clinical studies started in 2006. Currently, a

Phase IIb clinical trial is ongoing in patients undergoing myeloablative cord blood transplant for leukemia and other blood cancers. It is believed that this approach may have a limited outcome, since the progenitors have to be used in combination with cord blood transplantation and since the progenitors are unable to self-renew (albeit transiently).

As mentioned above, Magenta recently in-licensed a clinical stage asset from Novartis, MGTA-456 (formerly HSC835, or SR-1), which demonstrated increased expansion of cord blood stem cells in a Phase I/II study. The company is also exploring other ways to mobilise and expand these stem cells and apply gene therapy and gene-editing techniques for certain diseases. We understand that these plans are still at the discovery stage.

Furthermore, immunotherapy is very rapidly growing. The impressive results in blood and other cancers using CAR-T cells (Chimeric Antigen Receptor -T cells) (Jackson, Rafiq, & Brentjens, 2016) suggest immune cell therapies will play a significant role. However, it is unlikely that such therapies will completely replace the need for HSCT and indeed these approaches may well be complementary. Hu-PHECs provide a unique source of the patients own cells and may themselves play a substantial role in delivering gene-mediated therapies.

Intellectual property

The Hemogenyx CDX conditioning and Hu-PHEC technology are the subject of a number of filed patents yet to be granted, which have either been filed by or the rights licensed to Hemogenyx. Aruwon is not qualified to provide expert analysis on intellectual property. Analysis of the merits of these applications does not form a part of this report.

Reimbursement

HSCT is already a recognised and reimbursed procedure for a variety of diagnoses. Average pricing has been well reviewed (Milliman, 2014). Pressure on reimbursement is only likely to increase with an increased need to demonstrate real clinical benefits to justify pricing,

Market and Opportunity

There were, according to Worldwide Network for Bone Marrow Transplantation, around 60,000 procedures for the treatment of over 70 different diseases in the US and Europe (Passweg, Baldomero, Bader, & Bonini, 2016). Although HSCT is already one of the fastest growing procedures, there is a need to open up the therapy to older more vulnerable patients through gentler more effective conditioning, while at the same time meeting the increasingly unmet need for suitable donor cells.

Although at a preclinical stage of development, both Hemogenyx's product candidates have the potential to meet these needs and subsequently address substantial markets.

CDX Conditioning

While the continued development of RIC has expanded access to progressively older and more infirm patients, these are still unsuitable for at least one third of patients over 55 and an increasingly elderly population will only see the need for gentler treatments increase.

If successfully developed and found to be as effective and safe in man as it currently is in mice, we believe Hemogenyx's CDX bispecific antibody should have potential not only in the one third of patients over 55 who are currently ineligible for HSCT, but also in a substantial proportion of the majority of patients who currently receive the range of RIC regimens.

According to Milliman (Milliman, 2014) the average full cost, in the US, of an allogeneic HSCT is $930,600 and an autologous transplant at $378,000. Given that there were 12,460 autologous and 8,709 allogeneic (Milliman, 2014) transplants performed in 2014 the estimated market size for the full transplant procedure, from start to finish (including pre/post transplant care and drug therapy costs) is $12.8bn. There were 21,169 procedures in the US and a further 40,829 in Europe in 2014 at estimated average prices for CDX conditioning of $50,000 for Europe and $80,000 for the US would imply a total addressable market in Europe and the US of approximately $3.7bn.

Hu-PHEC Transplantation

Despite increased access to donor tissue through the establishment of Umbilical Cord Blood (UCB) banks, demand already outstrips supply. Numbers from the Health Resources Services Administration (HRSA) suggest that at least 60% of eligible patients in the US are unable to find an appropriately matched donor. This is a particular problem for mixed race or ethnic minority groups. Hemogenyx's potential to generate new sources of donor cells with Hu-PHEC from umbilical cord blood vessels and the liver has the potential to help meet the increasing demand from both allogeneic and autologous transplant candidates.

Umbilical Cord Hu-PHEC

While UCB held in blood banks has been increasingly seen as a valuable alternative to bone marrow or peripheral blood from registered donors, the numbers of HSC obtained from UCB are frequently too low, leading to delayed or failed engraftment, especially when comparing adult to child recipients. While this problem can be mitigated by using blood from two umbilical cords, this will obviously substantially increase the cost, double the problem of identifying matched donor cells and reduce the availability of UCB for other patients when the supply is already limited.

Supplementation of the cord blood with Hu-PHECs could make transplants for adults from single cords possible. This would substantially boost the availability of optimally matched cord cells, allowing more patients to be treated more easily. Hemogenyx has indicated that the process of Hu-PHEC isolation is relatively straightforward and the cells can be successfully frozen and stored. While this clearly needs to be properly established, the company is confident that it will be able to isolate, bank and retrieve Hu-PHECs on a routine basis.

According to Milliman, the average current cost of transplant procurement for allogeneic HSCT in the US is $55,700. With 8,709 transplants performed in 2014, this amounts to a total market in the US of $485m. With, according to the HRSA, around 20k patients seeking transplants, there are around 11k who are currently unserved, bringing the potential addressable market to approximately $1.1bn in the US alone. (This may be a conservative estimate, as the Milliman estimate of procurement cost is an average that may include transplant from available siblings at often be negligible cost. With two UCB units frequently used per adult at an average cost of $40,000 per UCB unit, the cost of procurement per transplant would be closer to $80,000.)

Liver Hu-PHECs

Hu-PHECS derived from liver could provide a powerful alternative to stem cells sourced either from bone marrow or peripheral blood for patients seeking autologous transplantation. Autologous HSCT is often associated with increased rates of relapse. This is thought to be at least partially due to the contamination of the infused stem cells with tumour cells. This contamination would be removed by the use of autologous liver Hu-PHECs, which could thus provide a safer alternative to bone marrow and peripheral blood.

Milliman estimates the cost of autologous transplant procurement to be $10,700. If clinical studies with Hu-PHECs indicate a significantly reduced risk of relapse, this would justify a pricing premium. Assuming that the procurement price rises to the same level as allogeneic, with 12,460 patients receiving autologous grafts in 2014, this would amount to a total market in the US of at least $694m.

While yet to achieve proof-of-principle, autologous liver Hu-PHECs also have the potential to be used as vehicles for gene therapy for the treatment of a large range of inherited, metabolic, immune and infectious diseases. Such applications would open up potential markets measured in the billions of dollars.

Product Synergy

There is clear synergy between the two products. Success in CDX conditioning should enable previously excluded patients to join the pool looking for donors. This will feed the need for additional supplies of donor material such as Hu-PHECs.

Opportunities and Risks

Hemogenyx has accumulated an impressive body of data, providing strong proof of principle for the company's scientific approach. The products in development address a substantial opportunity in what is already a large and rapidly growing market. While its two lead products are independently viable, there is also substantial potential synergy, with one broadening demand and the other safely and efficiently providing supply. The products are disruptive to existing therapies, but are compatible with existing treatment paradigms and thus do not require physicians to adopt radically new therapeutic approaches. A focus on high need orphan indications should help accelerate clinical development as well as passage along the regulatory pathway.

While the company looks well placed to move forward, risks and uncertainties are considerable. While the data from the mouse models are highly encouraging, these models are clearly imperfect and the data generated within them is frequently not reproduced safely in human studies. Human immunotherapy is a highly complex area, where products frequently run into unforeseen issues of safety and efficacy upon entering clinical trials in human subjects. Human immunotherapy is also currently a very rapidly evolving area. Given that it could be at least 5 years before the Hemogenyx products reach the market, it is possible that the developments in other areas of immune or cell therapy will make the technologies obsolete.

Personnel

Hemogenyx has assembled an excellent team that combines outstanding science with expertise in clinical and commercial development.

Board of Directors

Vladislav Sandler Ph.D. - Co-Founder and proposed Chief Executive Officer

Dr. Vladislav Sandler is the Co-Founder and CEO of Hemogenyx and a research Assistant Professor at the State University of New York (SUNY) Downstate. Dr. Sandler is a widely published stem cell scientist with decades of experience in scientific research. In particular, Dr. Sandler has extensive experience developing novel methods of direct reprogramming of somatic cells into functional and engraftable hematopoietic stem cells, as well as developing novel sources of pluri- and multi-potent cells.

Dr. Sandler has conducted his research in Israel, Canada and the United States, including at the Children's Hospital at Harvard Medical School, the Salk Institute for Biological Sciences, Harvard University and Albert Einstein College of Medicine. He also led a team of scientists at Advanced Cell Technologies, Inc. and was most recently on the faculty of Weill Cornell Medical College. While at Cornell, Dr. Sandler made the significant discovery that the cells that give rise to blood stem cells during mammalian development continue to exist after birth, and he developed the method of isolation of these cells from humans. As a result of this important work, Dr. Sandler was awarded the inaugural Daedalus Fund Award for Innovation at Cornell. He went on to found Hemogenyx in order to further pursue this significant scientific discovery and his dedication to the translation of science into clinical practice.

Dr. Sandler has published numerous peer-reviewed papers, and has received a number of awards and fellowships for his scientific research. Dr. Sandler received his PhD from the University of British Columbia. He is a member of the International Society for Stem Cell Research.

Dr Sandler will be appointed as the Company's CEO from Admission.

Lawrence Pemble – proposed Chief Operating Officer

After serving for six years in the Royal Marine Commandos, Lawrence Pemble has over the past six years developed experience in establishing, financing and developing new businesses.

He has led financing rounds, M&A activities, worked for public companies and has held executive roles, up to and including CEO, for start-up and private equity backed ventures, both in private and public capacities.

He has worked extensively in the Private Equity industry, where he has held executive positions in life science and technology focused companies, most recently a Director of Blackcomb Technologies Limited, a Canadian private equity firm focused on military electronics and in Bonsai Capital Limited, a life sciences focused Private Equity company where he is currently a Director. Prior to this, he held a number of managerial and development positions in resources companies, in the gold and oil and gas sectors.

Mr Pemble will be appointed as Chief Operating Officer from Admission.

Dr Robin Campbell - proposed Chairman

Robin Campbell, PhD has more than 30 years' experience working in the pharmaceutical industry with large companies (Shell Research, Beecham International (now GSK)), start-ups (Porton International, PafraBio) and in investment banking primarily in life sciences investment research (including Credit Suisse, Jefferies).

Currently his specialty is searching out investable opportunities in the broader life sciences sector, and helping smaller companies raise growth capital. Robin has helped list a number of companies onto AIM and other international exchanges, advised companies on secondary fundraisings, private equity raises, M&A and has a broad reach into institutional and retail investor networks.

Initial roles in industry with, inter alia, Shell Research and Beecham International (now GSK) encompassed R&D, international strategic marketing and market access. He has also worked with start-ups such as Porton International and Pafra Biopreservation in business development roles. As a pharmaceutical and biotech analyst, his experience extends back more than twenty years with a range of firms including Credit Suisse First Boston, Hoare Govett and Jefferies International and more recently he has acted in a consultancy role in relation to a range of life sciences IPOs, AIM introductions and M&A activity.

He has a degree in Microbiology from King's College London, and a Ph.D. in Immunobiology from Liverpool University. Dr. Campbell currently advises a number of private and listed businesses in respect to strategic and financial market opportunities.

Dr Campbell will be appointed as Chairman from Admission.

Alexis M. Sandler - Co-Founder and COO

Alexis M. Sandler is the co-founder of Hemogenyx, for which she has served as the Chief Operating Officer. An attorney with fifteen years of experience in intellectual property and copyright, Ms. Sandler handles day-to-day legal and operational matters for the Company.

Ms. Sandler began her legal practice in Los Angeles at Hogan & Hartson LLP (now Hogan Lovells), specializing in media and intellectual property law. She then worked for several years at Katten Muchin Rosenman LLP representing studios, production companies, television networks, technology companies and other major media companies in all aspects of entertainment, media and intellectual property law. For three years, Ms. Sandler worked as the Director of Business and Legal Affairs for a division of the Fox Entertainment Group, where she advised the company on important intellectual property, corporate and other legal and business matters. Ms. Sandler went on to become the General Counsel at a Smithsonian affiliate museum in New York City, and is currently the Associate General Counsel at The Museum of Modern Art and the Secretary of the Board of Directors of its affiliate institution, MoMA PS1.

Ms. Sandler received her AB from Harvard University, her JD from the UCLA School of Law and her MA from New York University. She is a member of the State Bar of New York and the State Bar of California.

Ms. Sandler will be appointed as a non-executive director from Admission.

Advisory Board

Hemogenyx has established an Advisory Board. The Advisory Board will provide the Company with objectives and external perspectives and will also raise the Company's profile. Details of the Advisory Board Members are as follows:

Sir Marc Feldmann – Scientific Advisor and Chairman of the Board of Advisors

Professor Sir Marc Feldmann studied medicine at University of Melbourne, followed by a PhD with Sir Gus Nossal at the Walter and Eliza Hall Institute on in vitro immune responses and immune regulation.

His subsequent work in London led to the generation of a new hypothesis for mechanisms of autoimmunity, linking upregulated antigen presentation and cytokine expression. Testing this hypothesis led to the discovery with colleague Sir Ravinder Maini of the pivotal role of TNFa in the pathogenesis of rheumatoid arthritis. This major discovery has revolutionized therapy not only of rheumatoid arthritis but other chronic inflammatory diseases, and helped change the perception of monoclonal antibodies from niche products to main stream therapeutics. This has led to much scientific recognition for example election to the Royal Society, the National Academy of Sciences USA and the Australian Academy of Science, and major prizes: Crafoord Prize of the Royal Swedish Academy of Sciences, Albert Lasker Clinical Research Award and Gairdner Award. His current interests are to work with colleagues to define new treatments for major unmet needs, e.g. fibrosis, fractures cancer and atherosclerosis. The other major interest is towards more cost-effective therapy and trying to get closer to a cure for rheumatoid arthritis.

Dr. Alexander Tarakhovsky, M.D., Ph.D. - Scientific Advisor

Born in the former USSR, Dr. Tarakhovsky received his medical degree from the Kiev Medical Institute in Ukraine in 1978, and his Ph.D. from the Institute for Oncology at the Academy of Science in Kiev in 1982.

He has worked as a research associate at the Institute for Oncology, the Cancer Research Center in Moscow and the Institute for Molecular Genetics in Tallinn, Estonia. In 1992, he became a Humboldt Fellow and later a Research Associate at the Institute of Genetics at the University of Cologne, in Germany; he was promoted to group leader in 1994, and to tenured

Professor and Head of the Laboratory for Lymphocyte Signalling in 1996. He moved that lab to The Rockefeller University in 2000 when he was appointed Irene Diamond Associate Professor; he was named tenured full Professor in 2003. The laboratory's current interest is to identify the epigenetic mechanisms of adaptive and innate immune responses.

The most significant achievements in this direction include the identification of the role of histone lysine methyltransferase Ezh2 in antibody repertoire formation, discovery of a novel nuclear PKCd signalling pathway that causes autoimmunity, identifying the novel signalling pathway that utilizes lysine methylation for signal-dependent lymphocyte activation and the discovery of functional histone-like sequences (histone mimics) in non-histone mammalian and viral protein.

Koen Van Besien, M.D.,, Ph.D. - Clinical Advisor

Dr. van Besien is a graduate of University of Leuven, Belgium and holds a PhD from the University of Maastricht in the Netherlands. He is currently a Professor of Medicine and Director of the Stem Cell Transplant Program at NYP-Weill Cornell College of Medicine.

Dr. van Besien has established a national and international reputation with several research and clinical interests. He has devoted considerable efforts at developing novel treatment strategies for patients with recurrent lymphoma, including the introduction of novel drugs and treatment in salvage therapy and in transplant conditioning regimens. He also has developed novel methods of transplantation for those patients who lack matching donors.

He has over 200 publications in peer reviewed journals. He is a member of the editorial review boards of the journals, Bone Marrow Transplantation and Biology of Blood and Marrow Transplantation. He is also Editor in Chief of the journal Leukaemia and Lymphoma, a publication that has a 2015 impact factor of 3.1.

Mark Pykett, VMD, Ph.D. - Business Development Advisor

Dr. Pykett is the President and Chief Executive Officer of Agilis Biotherapeutics, LLC and he has two decades of experience in the pharmaceutical industry.

Previously he served as Chief Executive Officer of Navidea Biopharmaceuticals, a precision medicine company focused on oncology and neurology. Prior to Navidea, Dr. Pykett was President and Chief Operating Officer of Alseres Pharmaceuticals, a biotechnology company focused on neurodegenerative and central nervous system disorders.

Before Alseres, Dr. Pykett held senior executive roles at several public and private companies, including CEO of Cytomatrix and President of Cygenics, focused on a range of therapeutic areas, indications and products. Dr. Pykett has also served as a Director of several public and private companies, and of the not-for-profit organization HealthBuilders, developing health infrastructure in central Africa.

Dr. Pykett received a B.A. degree from Amherst College, a V.M.D. and Ph.D. from the University of Pennsylvania, and an M.B.A. from Northeastern University, and completed post-doctoral fellowships at the University of Pennsylvania and Harvard University

Jules Mitchel Ph.D. - Clinical Trials Advisor

Dr. Jules T. Mitchel is President of Target Health Inc., a New York City based CRO with expertise in Regulatory Affairs, including FDA interactions and all submissions, Strategic Planning, Clinical Research Management, Biostatistics and Data Management, Medical Writing, Good Manufacturing Practices (GMP) and other support services to the pharmaceutical industry.

Dr. Mitchel has broad base pharmaceutical experience in drugs, biologics, devices and diagnostics including three NDA submission, many FDA meetings and IND/IDE submissions, study reports, manuscripts and strategic planning. Areas of expertise include but are not limited to, Women's Health, Dermatology, Antimicrobials, Pharmacokinetics, Rheumatology, Ophthalmology, Natural Products, Oral Care, Oncology and Regulatory Affairs. Dr. Mitchel has held industry positions at American Home Products, Pfizer Laboratories and Pfizer Consumer Health Care and academic positions at New York Medical College, Cornell University School of Medicine and NYU School of Medicine.

Boris Shor, Ph.D. Corporate Development Advisor

Dr. Shor is Executive Director, R&D and Scientific Partnerships at Immune Pharmaceuticals in New York City, where he oversees the discovery and development of novel antibody-based therapies for the treatment of cancer and inflammatory diseases. Before joining Immune Pharma, Dr. Shor was a group leader at the Oncology Research Unit of Pfizer in New York.

While at Pfizer, he led internal and external collaboration project teams to develop novel antibody-drug conjugates (ADCs) and supported Biological License Application (BLA) filings with worldwide regulatory authorities. Prior to that, Dr. Shor served as a senior scientist and a project team leader at the department of Oncology Discovery at Wyeth Pharmaceuticals, managing the discovery and characterization of novel small molecule kinase inhibitors for the treatment of cancer. Dr. Shor received a Ph.D. in Molecular and Cell Biology at the State University of New York and performed a postdoctoral fellowship in the Inflammation Research team at Johnson & Johnson Pharmaceutical R&D prior to joining Pfizer. He is currently a mentor to entrepreneurial academic researchers, early-stage biotechnology companies and is a life sciences investment advisor for a venture-capital fund.

Dr. Shor has nearly 15 years of experience in leading oncology discovery programs and external R&D partnerships at the large pharmas (Wyeth, Pfizer) and biotech startups (Immune Oncology, Hemogenyx, OmniCyte), with specific focus on preclinical development of small molecule inhibitors, biologics and nanoparticles. Most recently at Pfizer, Boris led cross-functional oncology research teams to develop novel antibody-drug conjugates and supported Biological License Application (BLA) filing for the late-stage therapeutics. Prior to that, Dr. Shor served as a project team leader at the department of Oncology Discovery at Wyeth Pharmaceuticals, managing the discovery and characterization of novel kinase inhibitors for the treatment of cancer. He currently serves on the

executive management team of early-stage biotech companies and is a life sciences investment advisor for venture-capital funds. Dr. Shor received a Ph.D. in Molecular and Cell Biology at the State University of New York and performed a postdoctoral fellowship in the Inflammation Research team at Johnson & Johnson Pharmaceutical R&D prior to joining Pfizer.

Research and Development Team

Dr Cristine Chisholm Ph.D., Scientist

Dr Chisholm received a PhD in molecular biology from the University of Maryland where her work was focused on the role of kinase regulation on tumour suppressor stability in prostate cancer.

She then continued to the NIH for a postdoc, utilizing drug repurposing screens to overcome chemotherapy resistance in BRCA1 mutant breast cancer by targeting specific transporters in breast cancer stem cells. While at the NIH, she also investigated metastatic signatures and the role of P13K/mTOR signaling in the cytoskeletal remodeling and motility of chemotherapy-resistant breast cancer stem cells.

She has over ten years of management experience in the biotechnology industry, at both incubators and large biotechnology companies as an R&D and new product development scientist in oncology and infectious disease.

Dr Rita Simone Ph.D., Scientist

Rita received her PhD in “Internal Medicine, Autoimmunity and Gastro-Enteric diseases” from the University of Genoa, Italy.

She then continued to the Feinstein Institute for Medical Research as a postdoctoral fellow where she established a xenograft murine model of Chronic Lymphocytic Leukemia and studied immunomodulatory drug effects in vivo. She has published more than fifteen peer-reviewed scientific papers.

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