TISSUE-ENGINEERED HUMAN ACCELLULAR BLOOD VESSELS FOR CORONARY ARTERY BYPASS GRAFTING

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INTRODUCTION

Coronary artery disease (CAD) is the narrowing of the major blood vessels of the heart with symptoms ranging from angina to myocardial infarction and death. Treatment includes medical therapy and procedures such as percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG). CABG is among the most common surgeries performed in the US (~400,000 surgeries per year) and has been shown to improve quality of life as well as survival. The primary conduits are left internal mammary artery (LIMA) and saphenous vein, which is used in 85-90% of CABG in the US. SVG patency at 1 year is reported to be as low as 75%, primarily due to thrombus or neo-intimal hyperplasia. Additionally, SVG harvest can result in surgical wound infection at the harvest site potentially leading to prolonged hospital stay, need for re-vascularization and limb-loss. Therefore, an unmet need exists for an advanced, readily available CABG conduit for the treatment of CAD.

The Human Acellular Vessel (HAV), developed at Humacyte, Inc., is an investigational tissue-engineered blood vessel consisting of human extracellular matrix (ECM) proteins. The HAV is created by culturing human vascular cells within a biodegradable scaffold under biochemical and biomechanical stimulation. The resulting tissue is then deacelurized to yield a mechanically robust and non-immunogenic HAV (Fig 1).1 The HAV has been shown to be remodeled by the recipient’s own cells to closely resemble native vasculature.2 In this study, we used a small diameter (3.5mm) HAV as a conduit for CABG in a baboon surgical model and investigated the in vivo remodeling of the human HAV in the baboon for up to 6 months.

DEVELOPMENT OF A BABOON SURGICAL MODEL OF CABG

Table 1. Outcomes of 3.5mm HAV CABG Conduits in Baboons

<table>
<thead>
<tr>
<th>Animal</th>
<th>Weight (kg)</th>
<th>HAV Lumen (mm)</th>
<th>TFFM (mmHg)</th>
<th>Implant Duration (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>30.0</td>
<td>10.0</td>
<td>5</td>
<td>2</td>
<td>Occluded</td>
</tr>
<tr>
<td>B2</td>
<td>30.0</td>
<td>7.3</td>
<td>20</td>
<td>9</td>
<td>Occluded</td>
</tr>
<tr>
<td>B3</td>
<td>28.1</td>
<td>7.5</td>
<td>17</td>
<td>0 (Surgical Complication)</td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>28.6</td>
<td>3.2</td>
<td>15</td>
<td>6</td>
<td>Occluded</td>
</tr>
<tr>
<td>B5</td>
<td>31.5</td>
<td>3.2</td>
<td>34</td>
<td>27</td>
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</tr>
<tr>
<td>B6</td>
<td>30.3</td>
<td>3.5</td>
<td>19</td>
<td>23</td>
<td>Patent</td>
</tr>
<tr>
<td>B7</td>
<td>37.0</td>
<td>2.0</td>
<td>25</td>
<td>17*</td>
<td>Patent*</td>
</tr>
</tbody>
</table>

*Deline phase angulation: 6 months

**Figure 3. CABG Surgical Model Development.** Baboon (Bb) B1 and B2 were implanted with an aorta-LAD HAV bypass (A, B) which was occluded shortly post-op due to size-mismatch. Animals Bb3-7 were implanted with an aorta-RCA HAV bypass (C, D) which resulted in improved success and patency out to 6 months.

IN VIVO LONGITUDINAL EVALUATION OF IMPLANTED HAV CABG CONDUTS

**Figure 4. Computed Tomography Angiography (CTA) 3D Reconstruction** Evaluation of HAV CABG conduits at 1 Month (A, B), 3 Months (C, D) and 8 Months (E, F) post-implantation. Non-invasive imaging of implanted baboons showed no dilation or significant stenosis of aorta/RCA HAV conduits through 6 Months.

**Figure 5. Following Surgical Implantation of Aorta-RCA HAV conduits on Day 0 (A), HAVs were evaluated by left heart catheterization at 1-2 weeks (B) and 6 Months (C) prior to HAV explant (D).** Catheter angiography imaging at 6 Months showed patent HAV CABG conduits in animals Bb5 and Bb7. Explanted HAVs were found to be well incorporated to host tissue.

**Figure 6. Histological evaluation of host remodeling.** HAV’s explanted at 6 Months from animals Bb5, Bb6 were stained by H&E (A, B), by Masson’s Trichrome (C), for collagen muscle actin(α-SMA, D, E) and von Willebrand Factor (vWF, D, E). Formation of neo- adventitia and infiltration of host cells(α-SMA) cells were observed throughout explanted HAVs. Presence of endothelial cells expressing vWF (white triangles, E) on the lumen were observed in 6-Month explants.

**Figure 7. Variation in Baboon Coronary Vascular Anatomy was observed by pre-operative CTA imaging.** Baboons were imaged before CABG to determine optimum distal target. Animals were shown to have right-dominant (A) and left-dominant coronaries with LAD-(B) and LCx-dominant (C) presentations.

BABOON CORONARY ANATOMY VARIABILITY

- Model development was challenging due to variability in coronary anatomy and HAV to host artery size-mismatch, but aorta-RCA configuration was most appropriate.
- The 3.5mm HAV was successfully used as a conduit in a baboon surgical model of CABG with sustained patency at 6 months.
- The HAV repopulated with host endothelial, smooth muscle, and neo-adventitial cells that removed the HAV conduit during the 6-month implantation.

**SUMMARY**

- Coronary artery disease (CAD) is the narrowing of the major blood vessels of the heart with symptoms ranging from angina to myocardial infarction and death.
- The Human Acellular Vessel (HAV) is an investigational tissue-engineered blood vessel consisting of human extracellular matrix (ECM) proteins. The HAV is created by culturing human vascular cells within a biodegradable scaffold under biochemical and biomechanical stimulation.
- Small diameter (3.5mm) HAVs were produced at Humacyte, Inc. by scaling down our investigational 6mm HAV platform. Healthy adult male baboons (Papio anubus) were acquired from Texas Biomedical (San Antonio, TX). Non-immunosuppressed baboons were surgically implanted with a 3.5mm HAV as a CABG conduit under cardiopulmonary bypass using standard surgical techniques. The bypassed native coronary was ligated proximal to the HAV anastomosis and flow through the HAV was confirmed by transthoracic flowmetry (TFFM). Baboons were given aspirin (3.5mg/kg) and clopidogrel (0.2-0.5 mg/kg) daily throughout the study.
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**REFERENCES**


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**DISCLOSURE INFORMATION**

These results are from a pre-clinical study. The authors employed at Humacyte, Inc. (IR墨, KMM, LEN, JNL, and APR) own stock or stock options in Humacyte, Inc.