Development of human organs with nanocomposite materials, bioactive molecules and stem cells technology

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Coronary Bypass Surgery

Segment of blood vessel, usually the saphenous vein in the leg, is taken from the patient to be used as the bypass graft.
# Market Potential for Medical Devices

<table>
<thead>
<tr>
<th>Application</th>
<th>Estimated Potential Market Size</th>
<th>Unmet Need</th>
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</thead>
<tbody>
<tr>
<td>CABG</td>
<td>$15 billion 100-800 thousand pat</td>
<td>Thrombosis, fibrinogen build up, vein graft weakness</td>
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<tr>
<td>Renal graft</td>
<td>$10 billion</td>
<td>Thrombosis and infection</td>
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<tr>
<td>Urinary Catheter</td>
<td>$10 billion</td>
<td>Infection, irritation,</td>
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<tr>
<td>Cardiac Valves</td>
<td>$12 billion 82 thousand/year in US</td>
<td>Thrombosis, Durability, rejection</td>
</tr>
<tr>
<td>Stent</td>
<td>$14 billion+</td>
<td>Thrombosis, rejection, fibrinogen build up</td>
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Background (Cardiovascular Bypass graft)

- 5-30% of patients do not have suitable vein

- Grafts made from PTFE or Dacron have primary patency rates of 20-30% for vascular bypass at 4-5 yrs\(^1,2\)

Cause of graft failure

1. Compliance mismatch$^{1,2}$

2. Thrombogenicity of the material$^{3-5}$

$^4$de Mel A, Biomacromolecules 2008;9:2969-79.
Matrix mixture added:
Rat tail type I collagen+
Porcine aortic SMC
Incubated and fed
>>> rapid radial contraction +

Precondition, typically
venous flow shear stress 7 days
arterial flow shear stress 14 days

EC graft + in vivo test

Tiwari A, Circ Res. 2003;93:1

SEM            EC Cell Expression, Immunostaining CD34, gene expression RT PCR

100 bp marker

100 bp marker

Static 1hr       Flow 1hr

PECAM-1

PECAM-1

COL-1

COL-1

TGF-β

TGF-β

GAPDH

GAPDH
Tissue Engineering with Human Cells age > 55

- Low burst pressure (80 mm Hg)
- Elderly cells very difficult to harvest & culture from vein or fat

- These and logistical problems make introduction of totally autologous TEVG in the foreseeable future for adult unlikely
Nanomedicine
Dr Bala Ramesh, Senior Research Fellow
Miss Shirin Ghadiri, PhD student
CNT & Graphene

RoboTroop
The US Army's vision for 2050. Many of these technologies are already under development.

Bulletproof Suit

Cardiac Patch
R&D Nanoparticles

Silver & Gold

Superparamagnetic

inhibit microbial growth
Thermal treatment of cancer

Pre-treatment

During treatment

Post-treatment
Developed a family of bioactive nanocomposite materials, example:
Based on POSS+poly(carbonate-urea)urethane (PCU)

trans-Cyclohexane
Diol Isobutyl-
Polyhedral
Oligomeric
Silsesquioxane
(POSS)

Part of structure containing POSS molecule covalently attached to the polymer chain
Polycarbonate soft segment
MDI / Ethylenediamine urea hard segment
Development of two families of bioactive nanocomposite materials.

A. Control PCU 2% POSS-PCU 8% POSS-PCU

B. Tensile strength vs. tensile strain

C. Zeta potential vs. pH

D. Absorbance vs. wavelength
AFM

Superhydrophobic nanomaterial coating for clothes could reduce scalding injuries
SEM further shows HUVECs adhering to the grooved surface
Miss Debra Chong, PhD UCL
Prof Dalby, University of Glasgow
Figure 4. A. Freshly isolated adipose-derived stem cells; B. ASCs cultured in media for 7 days; C. ASCs after 7 days of culture, appearing to begin neovessel formation.
In collaboration with Professor Ferretti, UCL

**autologous stem cells and nanoscaffolds for cartilage reconstruction**

- POSS-PCU + ADSCs
- ADSCs (adipose tissue derived stem cells)

encasement by vasculature

bionanounoscaffold
cartilage differentiation

ear
nose
trachea

adipose tissue
12 weeks subcutaneous post-implantation

A. POSS-PCU (150-250 μm)
B. POSS-PCU (50-100 μm)
C. Medpor®
Growth factors

Scaffold seeded with cells attached

Scaffold placed in bioreactor for culture in chondrogenic medium

Construct placed underneath patient skin on the forearm to bio-integrate and vascularise.

Cartilage is harvested from the arm and sutured in place to reconstruct the nose. A skin graft can then be used to complete the surgery.

Tissue Engineering

Tina Sedaghati, PhD Student
We developed a bypass graft with a base on Poly(carbonate-urea)urethane. Bonded with bimolecules.

SEM: Honeycomb Structure

Cells (SMC, EC)

Moieties (E.g. - RGD, Heparin)

Acrylamide attached to activated surface from which was abstracted hydrogen leaving OH

Elastic basement layer (polymer)

Compliant arterial prosthesis design

Obtaining long-term compliance is difficult as to date PU based grafts have relied on overall external dilation which is negated by perivascular in-growth.

The design approach used here has been to develop a prosthesis that maintains compliance and pulsatile flow *in vivo* by enabling the transmission of energy and a better quality of flow.

This is achieved via the honeycomb structure which accommodates increases in volume without the need for external dilation—a mechanism of wall compression.

ESEM cross-section (×50) and surface (×250) micrographs
Biocompatibility Studies

In Vivo Studies:

- 36 months in a sheep model for biocompatibility studies
- 9 months in a sheep model as a bypass graft
- Undergone all biocompatibility tests to the international standard ISO10993.
We have used silica nanoparticles to “couple” RGD into polymer

Aerosil 504 is fumed silica reacted with Hexamethyldisilazane and Aminosilane to form a hydrophobic fumed silica with functional surface amine groups.
Capturing Stem Cells from Blood

1. Mobilisation of Bone Marrow Progenitor Cells
2. Homing of EC/EPC to vascular graft
3. EC/EPC adhesion
4. Proliferation and differentiation
5. Mature endothelium

Blood Flow

Vascular graft
B and M Mode imaging of longitudinal vessel segment

Acquisition of induced radiofrequency signal received from anterior and posterior walls

Tracking of signal over time to generate distension curves
Elasticity/compliance $C = \frac{(D_s - D_d)}{(D_d(P_s - P_d))}$
Viscous component $\sin(\phi)$
Coronary and vascular artery bypass

Clinical trials

Preclinical test

Manufacture

Mean Pressure (mmHg)

Compliance (% per mmHg x 10^{-2})

- POSS-PCU
- Artery (anisotropic)
- Vein
- Dacron
- PTFE

Bypass grafts
(5 cm, ID 5 mm, WT 0.8-0.9 mM)
Heart valve through blood vessels

In collaboration with; Dr Gaetano Burriesci, UCL
Postdoc: Dr Ben Rahmani
Transcatheter Aortic Valve

Nitinol stent

- Self-expandable Nitinol frame
- One-piece polymeric membrane
- Fully retrievable and repositionable
- Multi-stage and controlled collapse & expansion
- Polymeric skirt to prevent paravalvular leakage
- Enhanced anchoring with no need for excessive radial force

POSS-PCU leaflets

Outflow

Inflow
A number of sealing strategies were proposed to reduce paravalvular leakage.
Opening phase

SSAV 150µm

Control (Epic™)

(a) (b) (c) 86 %

(d) (e)

(f) (g) (h) 47 %

(i) (j)

Pressure (mmHg)

Systolic  Diastolic  Systole
Stent design optimisation

Areas of high stress concentration

Size 23

- 1200 - 1400 MPa
- < 1000 MPa
- ~ 1000 – 1100 MPa
- < 1100 MPa

Size 29

- 1200 - 1400 MPa
- < 1000 MPa
- ~ 1200 – 1300 MPa
- ~ 1200 MPa
- Full repositionability and retrievability
  - 18 Fr delivery system
  - 3 stage valve expansion through three control lines
  - After full deployment catheter can be moved away and valve functionality verified.
  - If necessary, catheter can be readvanced and the valve safely recollapsed and repositioned.
  - Once the procedure is satisfactorily completed, the control lines can be released and extracted
TRISKELE Transcatheter Heart Valve
TRISKELE Transcatheter Heart Valve
First animal implant in ovine model (≈ 50 kg) in May 2013, off-pump via brachiocephalic approach in orthotopic position, using continuous ultrasonic and fluoroscopic guidance.

Three valves of different sizes successfully implanted and retrieved, after assessing positioning and haemodynamic performance.

No interference of coronary blood flow for two smallest sizes, and good acute valve function with no significant regurgitation.
A) No interference of coronary blood flow was observed;  
B) the valve was self-aligned owing to its outflow protrusions which expand to assist optimal positioning.
1. Patient MRI + glass moulding of exact tracheal replica

2. Synthesis of POSS-PCU based trachea / patient-own stem cells

2. Surgical implantation of tracheal construct
Dr Karla Chaloupka, Zurich University Hospital
Research and Development
MHRA / FDA
Funding
Industry
Commercialisation
NanoRegMed Ltd, London, UK

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