Embracing technology: The future of Hepatology

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Johannesburg
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Disclosure

Med tech inventor and doctorpreneur
Liver transplantation in children

- Excellent outcomes have made liver transplantation the treatment of choice in many end-stage liver disorders.
- The field is evolving to include new indications such as metabolic diseases.
- With excellent short term outcomes the focus in children is to achieve a long and happy life with a healthy liver graft.
Liver transplantation in children

- Challenges remain with regards to very long-term graft health and immunosuppression side-effects
  - Longest survivor 40 years
  - Graft fibrosis common 10 year protocol biopsies
  - Attrition in patient and graft survival on very long term outcomes

- Social challenges also remain with disparities in organ supply and demand and unequal access to high quality healthcare
#embrace
Four Paradigms

• Cells
• Precision medicine
• Robotics
• Patient empowerment
  – Health education
  – Adherence
  – Disease prevention
  – Workflow reorganisation
Cells

- Muscle Cells
- Blood Cells
- Nerve Cell
- Cardiac Cell
- Intestinal Cells
- Liver Cells
Hepatocyte Tx

• Synthetic and detoxifying function for few weeks
• Bridge to transplantation
Microbiological Testing
“Mincing” Digested Tissue
Checking Cell No. and Viability
(Trypan Blue exclusion technique)
Hepatocytes in beads

• Function for a few weeks
• No immunosuppression
• Easier access sites in coagulopathic patient
Hepatocyte Encapsulation

250µm

HCs/1.5% alginate

1.2% CaCl₂

Reaction vessel

400-450µm Ø
LIVER TREATMENT

Immune Cells

Courtesy BBC
CELL FUNCTION AND VIABILITY

MTT RESULTS OF MICROENCAPSULATED HEPATOCYTES CULTURED IN WILLIAM'S E MEDIA

<table>
<thead>
<tr>
<th>Time</th>
<th>Average O.D. at 630nm per 100mg Beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>24Hrs</td>
<td>1.0</td>
</tr>
<tr>
<td>48Hrs</td>
<td>1.2</td>
</tr>
<tr>
<td>72Hrs</td>
<td>1.1</td>
</tr>
<tr>
<td>1 week</td>
<td>0.9</td>
</tr>
</tbody>
</table>

UREA PRODUCTION OF ENCAPSULATED HEPATOCYTES CULTURED IN WILLIAM'S E MEDIA

<table>
<thead>
<tr>
<th>Time</th>
<th>Urea concentration (mg/dL) per 100mg Beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>24Hrs</td>
<td>0.4</td>
</tr>
<tr>
<td>48Hrs</td>
<td>0.6</td>
</tr>
<tr>
<td>72Hrs</td>
<td>0.5</td>
</tr>
<tr>
<td>1 Week</td>
<td>1.0</td>
</tr>
</tbody>
</table>

FACTOR VII PRODUCTION OF ENCAPSULATED HEPATOCYTES CULTURED IN WILLIAM'S E MEDIA

<table>
<thead>
<tr>
<th>Time</th>
<th>FVII concentration (ng/ml) per 100mg Beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>24Hrs</td>
<td>2.0</td>
</tr>
<tr>
<td>48Hrs</td>
<td>3.0</td>
</tr>
<tr>
<td>72Hrs</td>
<td>1.5</td>
</tr>
<tr>
<td>1 Week</td>
<td>3.5</td>
</tr>
</tbody>
</table>
First in man - March 2011
Microbeads

Before Tx

Retrieved Microbeads

Albumin Production

Post-retrieval

Days in culture

Albumin (ng/mg protein)

16G cannula

Microbeads passing through tip of cannula into peritoneal cavity

Syringe containing hepatocyte microbeads

Albumin Production

[Post-retrieval]

<table>
<thead>
<tr>
<th>Days in culture</th>
<th>Albumin (ng/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>300</td>
</tr>
<tr>
<td>D7</td>
<td>200</td>
</tr>
<tr>
<td>D14</td>
<td>100</td>
</tr>
</tbody>
</table>
Progress in stem cell-based therapy for liver disease

Goshi Shiota, Noriko Itaba

First published: 17 June 2016   Full publication history
DOI: 10.1111/hepr.12747   View/save citation

Cited by (CrossRef): 6 articles   Check for updates

Citation tools
Cell source of stem cell-based therapy for liver disease
Hepatocytes from somatic cells by direct reprogramming can be transplanted, and hepatocytes differentiated from induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and liver progenitor cells are also transplantable.

Both HSCs and MSCs can be infused directly to the liver.

Hepatocytes obtained from somatic cells, iPSCs, MSCs, and liver progenitor cells can be transplantable in the forms of liver bud, perfusion decellularization/recellularization systems, and hepatic cell sheets.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Type of infused cells</th>
<th>Patient group (n)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al.⁹⁴</td>
<td>Cohort</td>
<td>BM-MSCs</td>
<td>Primary biliary cirrhosis (10)</td>
<td>Improvement in serum ALT, AST, γ-GTP, and IgM</td>
</tr>
<tr>
<td>Jang et al.⁹⁵</td>
<td>Cohort</td>
<td>BM-MSCs</td>
<td>Alcoholic cirrhosis (12)</td>
<td>Improvement in MELD score and liver histology</td>
</tr>
<tr>
<td>Salama et al.⁹⁶</td>
<td>RCT</td>
<td>G-CSF followed by BM-MSCs</td>
<td>End-stage liver disease (20 treatment, 20 control)</td>
<td>Improvement in MELD score and Child–Pugh score</td>
</tr>
<tr>
<td>Wang et al.⁹⁷</td>
<td>Cohort</td>
<td>UC-MSCs</td>
<td>Primary biliary cirrhosis (7)</td>
<td>Decrease in alkaline phosphatase and γ-GTP, alleviation of fatigue and pruritus, decrease of ascites</td>
</tr>
<tr>
<td>Mohamadnejad et al.⁹⁸</td>
<td>RCT</td>
<td>BM-MSCs</td>
<td>Liver cirrhosis (15 treatment, 12 placebo)</td>
<td>No changes in MELD score, Child–Pugh score, albumin, prothrombin time, transaminases, or liver volumes</td>
</tr>
<tr>
<td>Amin et al.⁹⁹</td>
<td>Cohort</td>
<td>BM-MSCs</td>
<td>Liver cirrhosis (20)</td>
<td>Decrease in bilirubin, AST, ALT, prothrombin time and INR, increase in albumin, improvement in MELD score</td>
</tr>
<tr>
<td>Zhang et al.¹⁰⁰</td>
<td>Case–control</td>
<td>UC-MSCs</td>
<td>Liver cirrhosis (30 treatment, 15 control)</td>
<td>Improvement in liver function and MELD score, reduced ascites</td>
</tr>
<tr>
<td>Shi et al.¹⁰¹</td>
<td>Case–control</td>
<td>UC-MSCs</td>
<td>Acute-on-chronic liver failure (24 treatment, 19 control)</td>
<td>Improvement in liver function and MELD score, increased survival rates</td>
</tr>
<tr>
<td>El-Ansary et al.¹⁰²</td>
<td>Case–control</td>
<td>BM-MSCs</td>
<td>Liver cirrhosis (15 treatment, 10 control)</td>
<td>Improvement in MELD score and albumin</td>
</tr>
<tr>
<td>Peng et al.¹⁰³</td>
<td>Case–control</td>
<td>BM-MSCs</td>
<td>Liver failure (53 HBV, 105 control)</td>
<td>Improvement in albumin, bilirubin, prothrombin time, and MELD score</td>
</tr>
<tr>
<td>Amer et al.¹⁰⁴</td>
<td>Case–control</td>
<td>Cultured BM-MSCs stimulated to hepatic lineage using HGF</td>
<td>End-stage liver cell failure (20 HCV, 20 control)</td>
<td>Improvement in MELD score and Child–Pugh score</td>
</tr>
<tr>
<td>Kharaziaha et al.¹⁰⁵</td>
<td>Cohort</td>
<td>Cultured BM-MSCs</td>
<td>Liver cirrhosis (8)</td>
<td>Improvement in liver function, MELD score, creatinine, and prothrombin complex</td>
</tr>
<tr>
<td>Mohamadnejad et al.¹⁰⁶</td>
<td>Cohort</td>
<td>Cultured BM-MSCs</td>
<td>Liver cirrhosis (4)</td>
<td>Improvement in MELD score and serum creatinine</td>
</tr>
</tbody>
</table>
BM derived MSC engineered hepatic cell sheets

- Orthotopic transplantation of human MSC-engineered hepatic cell sheets on areas of acute liver injury in mice
  - enhanced liver regeneration
  - suppressed liver injury
  - Improved survival rates
Human MSCs are engineered then transplanted as hepatic cell sheets on the liver surface at an area of acute injury. Activation of complement C3 and its downstream signals was observed in association with augmented thioredoxin oxidation and reduction cycle and epidermal growth factor receptor (EGFR) phosphorylation (p).
Precision medicine

The genomic and epigenomic revolution
King’s Genome Diagnostics forum

The road to precision medicine; the impact of genetic tests on the diagnosis and treatment of gliomas

Professor Safa Al-Sarraj
Clinical Director of Precision Medicine and Specialised Laboratories

5th December 2017, 1-2pm
Western Education Centre Classroom 3
Multidrug resistance 3 protein

- $ABCB4$ gene on chromosome 7q21
- ABC transporter family
- Canalicular membrane of hepatocytes
- Phospholipid transporter
- Protects biliary system from bile acids
Severe MDR3 deficiency

• So-called PFIC3
  - Paediatric onset
  - Autosomal recessive inheritance
  - Raised serum bile acids / serum γGT
  - Biliary cirrhosis and liver failure
Late onset MDR3 deficiency

- Low phospholipid associated cholelithiasis (LPAC)
  - Stones / biliary sludge

- Intrahepatic cholestasis of pregnancy (ICP)
  - 3rd trimester maternal cholestasis/foetal distress
  - Resolves after delivery
• Sequencing cholestasis genes yields nucleotide variants of unknown significance
• “Postgenomic” study
• How do sequence variants in ABCB4 (encoding MDR3) provide insight into how mutations impact the function of the encoded protein?
Current

- The most common sequence abnormalities are missense variants which are found along the entire gene length
- Algorithms are used to classify variants into benign polymorphisms or mutations
  - Likelihood that variants will impair function of encoded proteins
  - Prevalence of variants in the normal population
  - Conservation of nucleotide sequences across species
  - Typical mutation-causing changes (nonsense/frame-shifting deletions)
• Study looked at the biological consequences of 12 variants in 9 children with PFIC3

• Functionally, all but 4 mutants produced abnormal phosphatidylcholine secretion
  – 2 of the 4 had normal cannalicular expression of MDR3 but reduced protein stability
  – The other 2 had no discernible defect = polymorphisms
• Variants were classified I-V according to severity
  – I - nonsense or frame-shifting deletion
  – II – protein maturation impact
  – III - protein activity impact
  – IV – protein stability impact
  – V – no discernible defect

• Of interest, one of the class V variants had previously been proposed to be deleterious on the predictive algorithms
Precision medicine?

• Not yet

• We are learning the relevance of mutation variants
• But there is a need for studies screening pharmacologic agents targeting the mutant protein to restore function

• We know the mutation and the variant, once we know the drug then we can select treatments based on the patient’s genomic makeup.
Robotics
Patient empowerment

Health education
Adherence
Disease prevention
Workflow reorganisation
Development of a smartphone app and synchronised web-based technology for secure self-monitoring in the intestinal failure and bowel transplant population

Dr Jonathan Hind
Consultand Paediatric Hepatology,
Intestinal Rehabilitation and Transplantation
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July 2015
Background

• Children with intestinal failure and post small bowel transplant:
  – Medical issues which need specialist attention
  – May live far from health services
  – Communication issues
  – Potential for errors
  – Late reporting of medical problems

• Smartphone apps for health:
  – Health education
  – Self-monitoring
  – May encourage early detection of medical problems
  – Potential for expedited discharge of patients from hospital

• Very few smartphone apps available which synchronise self-monitoring data tracking with healthcare professionals
• None for the bowel transplant population
Service Development
Patient-centred approach

• Patient/carer requests:
  – Remove paper-monitoring/diaries
  – Reduce need for travel/time off work
  – Easier communication with transplant centre
  – Communication across boundaries
  – Feel secure

• Staff needs:
  – Close knowledge of patient status
  – Reduced admin work
  – Quick access to patient data
  – Easier communication with patient
  – Easier communication with shared-care teams
Aims

• Promote health knowledge
• Promote self-monitoring
• Promote input into own management
  – Reduce need for travel to clinics
• Encourage early detection of problems
  – See patient when they need to be seen

• Allow easy communication
• Facilitate more effective clinic appointments/telephone calls
  – Improve staff working patterns

• Be low cost
  – Use devices which most patients already had
  – Reduce need for paper
• Use innovative technology
Technology development process

• Paediatrician, IT manager, digital entrepreneur

• 2 years collaborative work
  – Wide-ranging input from patients and staff
  – Design innovative technology solution
    • Crowdsourcing
    • Web competitions
    • Case modelling
  – Design functionality, refine, then reiterate - cycle
    • User narratives through the technology

• Commissioned technology design company
  – Further iterations

• Release as test to “superusers”
  – Further iterations/bug resolution

• Release as pilot to specific patient group
  – Further refining/iterations/bug resolution

• 2015 Release on app store and Google Play
The app

HEALTH TOUCH

TRACKERS

MESSAGES

CARE NETWORK

MEDICATION

SETTINGS
Tracking health parameters
Patient at the centre
Built in health education
The web technology
# Your patients

These are all the app users that have joined your care network and are sharing their details with you. If you want to add someone new then go to Care Network and send them an invite.

## LIST OF PATIENTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Email</th>
<th>Gender</th>
<th>DOB</th>
<th>Trackers</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allard, Rhianna 1231231231</td>
<td><a href="mailto:joonas.verdes@yahoo.co.uk">joonas.verdes@yahoo.co.uk</a></td>
<td>female</td>
<td>24/06/2010</td>
<td>Blood pressure, Heart rate, Oxygen saturation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluid output</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool type, Dyspnea</td>
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<tr>
<td>Atkinson, Matt 1111111111</td>
<td><a href="mailto:matthew.atkinson@idesign.co.uk">matthew.atkinson@idesign.co.uk</a></td>
<td>male</td>
<td>31/05/1987</td>
<td>Blood pressure, Heart rate, Oxygen saturation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heart rate</td>
<td></td>
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<tr>
<td>booker, Nina</td>
<td><a href="mailto:nina-neil@hotmail.co.uk">nina-neil@hotmail.co.uk</a></td>
<td>female</td>
<td>10/01/1986</td>
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<tr>
<td>hilden, Jessie-John</td>
<td><a href="mailto:amy.henardout@icloud.com">amy.henardout@icloud.com</a></td>
<td>male</td>
<td>18/08/2013</td>
<td></td>
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</table>
Outcome (patients)

- All 5 patients discharged home between December 2014 and February 2015 on HPN or post bowel transplant were offered to participate
- All consented and all use the app
- All track health parameters regularly

- Initial feedback is strongly positive
  - Feel more in control
  - Feel more secure with team
  - Easier communication, Faster communication
  - Reduced need for paper and for calculations

- Negative comments were related to bugs found in the technology and to the need for further functionality and development
### Fluid Output

<table>
<thead>
<tr>
<th>Frequency</th>
<th>On</th>
<th>At</th>
<th>Fluid output</th>
<th>Min</th>
<th>Max</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>daily</td>
<td>09:00:00</td>
<td></td>
<td></td>
<td>400</td>
<td>1000</td>
<td>ml</td>
</tr>
</tbody>
</table>

### Medication

- **Amlodipine**
  - 5.5mg once daily 7pm

- **Atenolol**
  - 5mg twice daily 7am, 7pm

- **Captopril**
  - 30mg x 3 times a day 7am, 3pm, 11pm

- **Dipyriramol**
  - 45mg x 2 times daily 9pm, 9am

- **Levetiracetam**
  - 425mg <2 daily, 7am, 7pm

- **Loperamide**
  - 1mg x 2 times a day 7am, 7pm

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid output</td>
<td>486 ml</td>
<td></td>
</tr>
<tr>
<td>Fluid output</td>
<td>103 ml</td>
<td>Yesterday @ 09:00</td>
</tr>
</tbody>
</table>
Outcome (staff)

• Core members of the intestinal rehabilitation and transplant team have been using the web application since December 2014

• Initial feedback positive
  – Greater knowledge of the status of the patients
  – Easier communication for routine needs
  – Easier management of multiple medications
  – Time saved on telephone calls
  – Quicker discussion and decision making during weekly clinical MDM

• Concerns include
  – Time taken to train patients in app use
Privacy, Security & Consent

Management of Patient Data and Consent

- Health Touch data is owned by the patient, who enters tracking and medication data and notes on their smartphone or tablet.
- Patients can then consent to share data with healthcare professionals of their choice.
- Patients can withdraw consent to share their data at any time.

The consent message is clear and simple; patients must actively agree for their data to be shared.

Patient Data Privacy and Security

Data is protected by user ID and password in the mobile app, and is also protected in transit using Transport Layer Security (TLS) encryption and protected in storage by AES-256 encryption and strong password protection, housed in facilities using physical security measures. Health Touch Ltd also works to a clear, documented privacy policy, available at our website https://healthtouch.org.uk
Where are we now?

• Kept low cost and free to the patient
• Used in more services
  – Tertiary intestinal failure
  – Tertiary Fabry’s disease
  – Primary care GPs
  – Community weight loss programme

• Charity funding of “patient passport” page in response to request from patients

• Next stage enhanced medication adherence and repeat prescription functionality
Conclusions

• Stem cells
• Precision medicine
• Patient empowerment
  – Health education
  – Adherence
  – Disease prevention
  – Workflow reorganisation