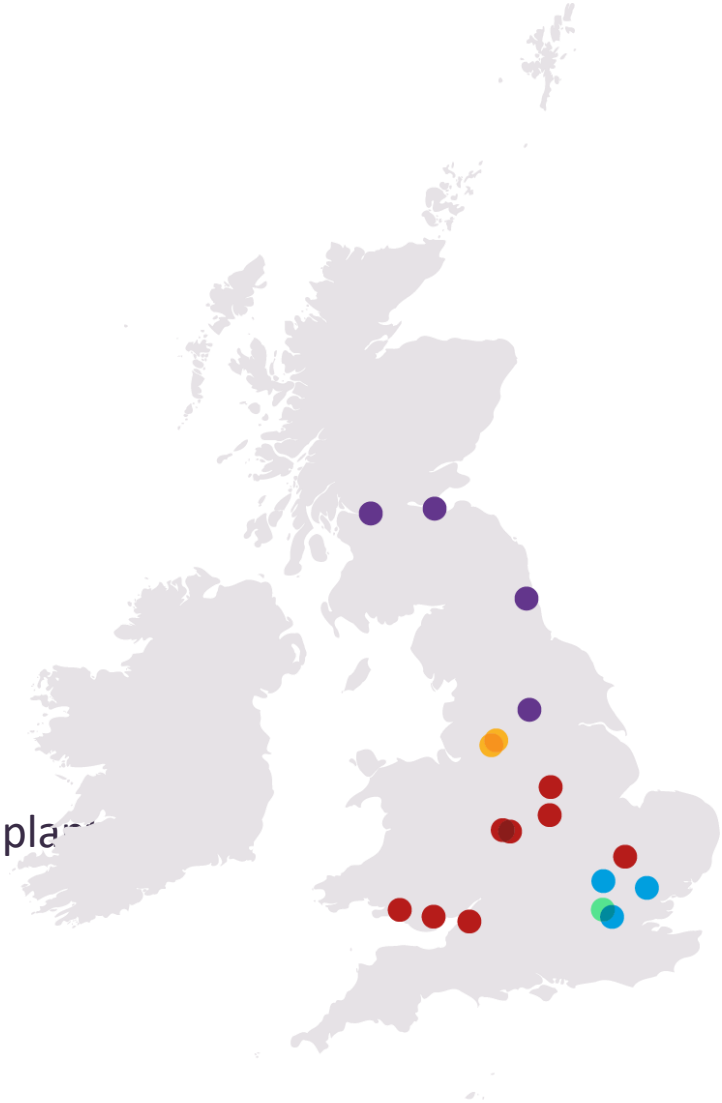
Advanced Therapy Treatment Centres

LONDON ADVANCED THERAPIES



ATMPs in paediatric haematology

Prof Rob Wynn
Consultant Paediatric Haematologist & Director of Paediatric Bone Marrow Transpla
Programme

Chaired by Ian Hollingsworth
ATTC programme manager, Cell and Gene Therapy catapult

Funded by

INDUSTRIAL STRATEGY

UK Research and Innovation

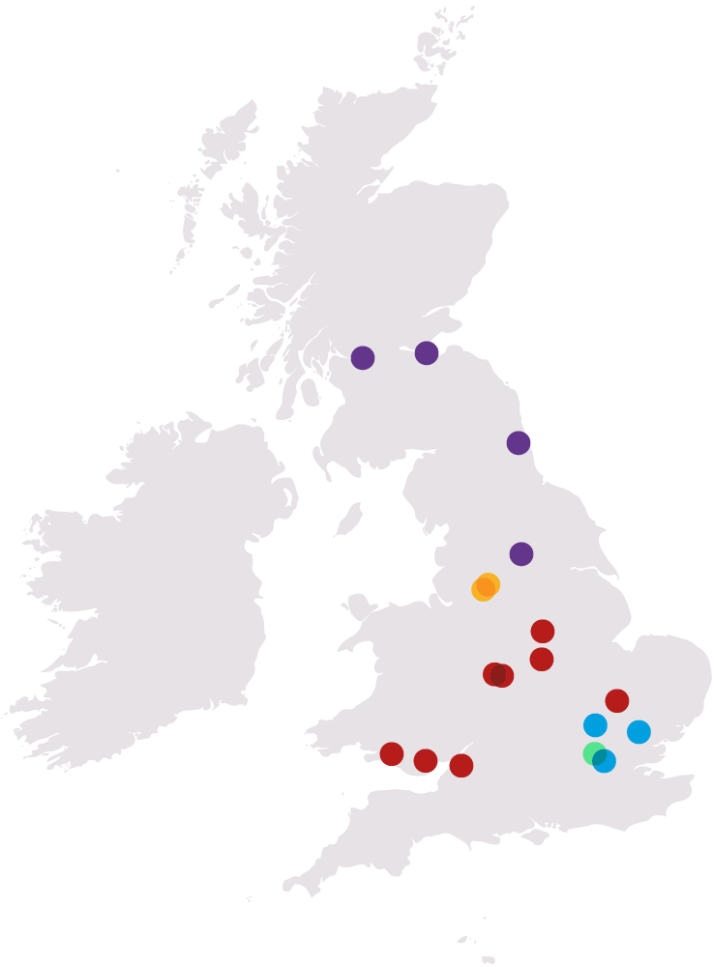
Coordinated by

CATAPULT Cell and Gene Therapy

Who are LAT and the ATTCs?

- The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund
- London Advanced Therapies (LAT) is funded by Research England
- The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.
- This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic
- Find out more at https://www.theattcnetwork.co.uk/

Please add questions to the chat box as we go along



MANCHESTER 1824

The University of Manchester

Central Manchester University Hospitals NHS
NHS Foundation Trust

Stem cell and Gene therapies in Paediatrics in Manchester

Rob Wynn, BMT, RMCH and University of Manchester

Summary of Talk

- My disclosures are those of an (NHS) transplant physician, of a clinician, rather than those of a laboratory scientist
- The future arises from our recognition of the utililty of stem cell and gene therapies in correcting our diseases, the diseases we see on our wards, and in our patients
- Imperative that clinicians are involved in this science of bench-to-bedside translation, as it builds on the successes or failures of previous therapies
- For me, it was work in BMT that leads to newer therapies. Where BMT works? Where does it not work? Why does it not work? What are its toxicities?
- Clinicians will run the trials and understand the regulatory process that accompany the introduction of these therapies

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The University of Manchester

Summary of Talk

- GENE THERAPY in genetic diseases and in cancer therapies
- STEM CELL therapies
- Our current and future work in BMT in Manchester
- This field as part of our future

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- Metabolic SC GT programme
- CAR-T and cancer gene therapy programme
- MSC and inflammatory disease, and metabolic bone disease gene therapy programme

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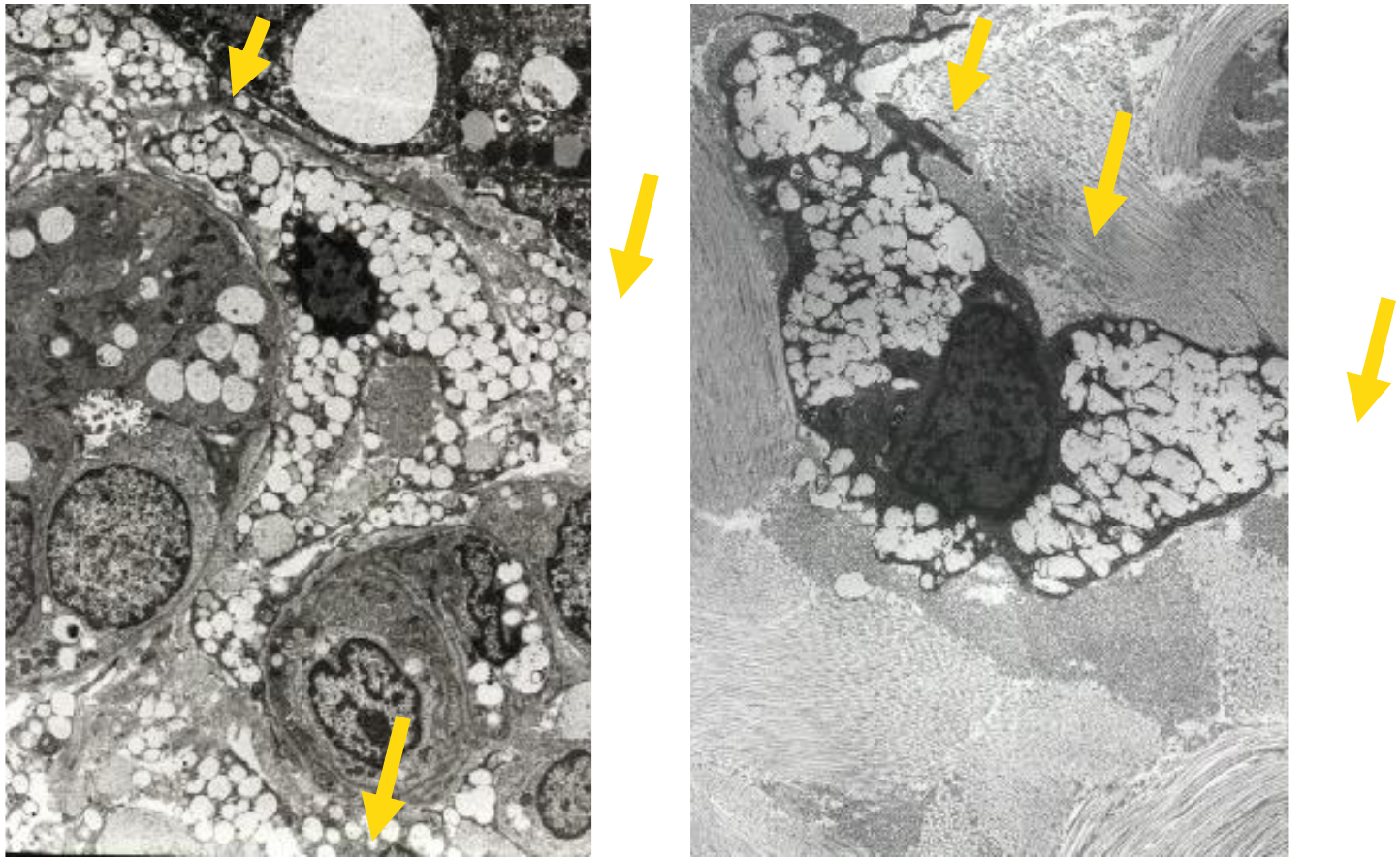
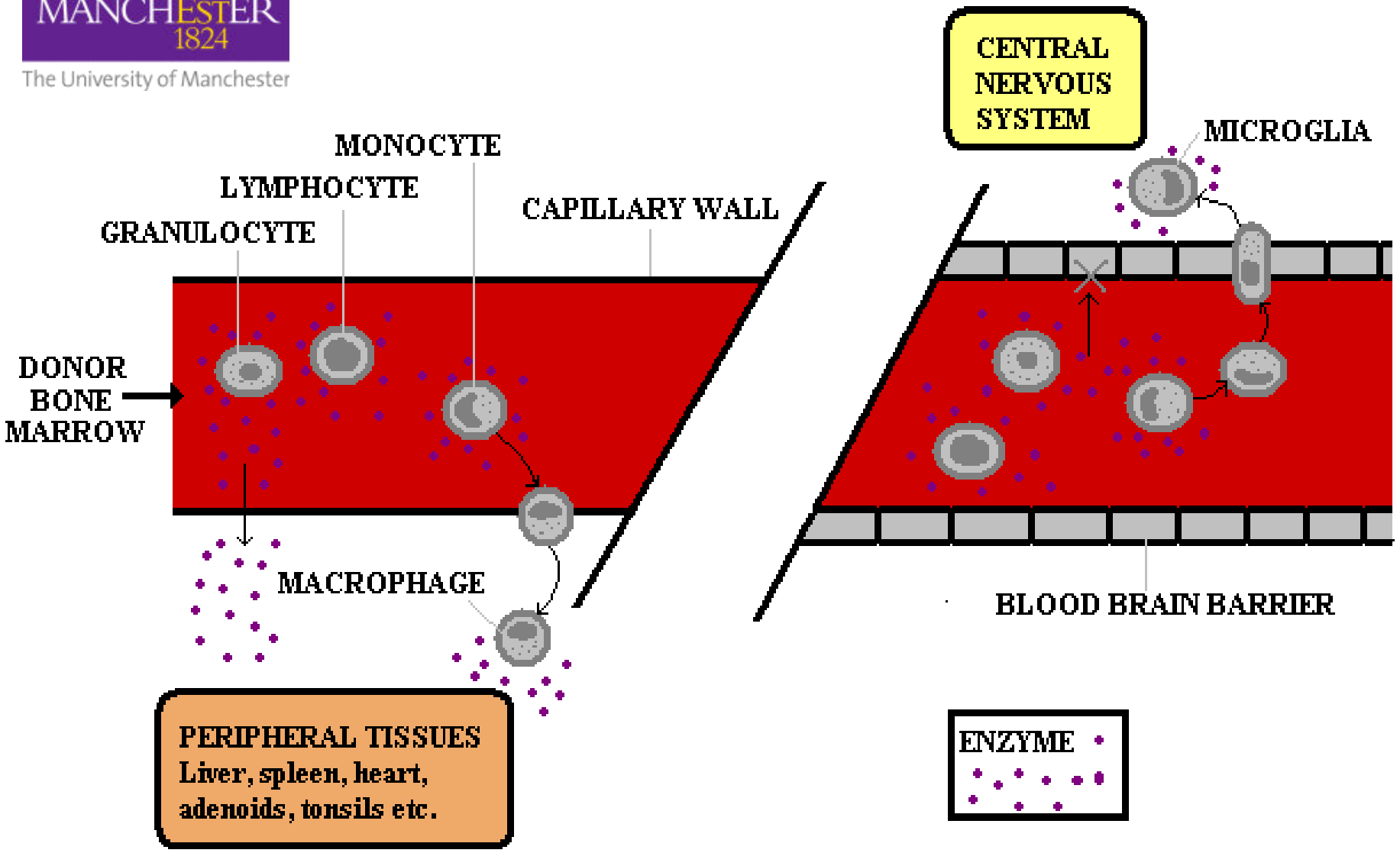
Lysosomal Storage of GAGs




MONOCYTE
LYMPHOCYTE
GRANULOCYTE
CAPILLARY WALL
DONOR BONE MARROW
MACROPHAGE
PERIPHERAL TISSUES
Liver, spleen, heart, adenoids, tonsils etc.
CENTRAL NERVOUS SYSTEM
MICROGLIA
BLOOD BRAIN BARRIER
ENZYME

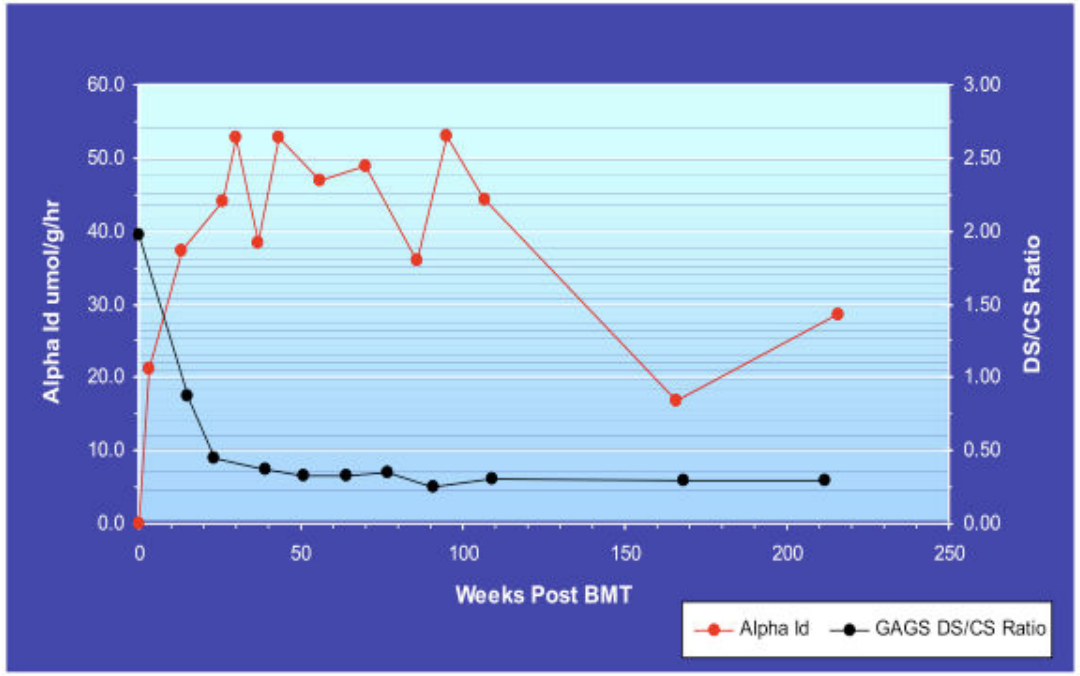
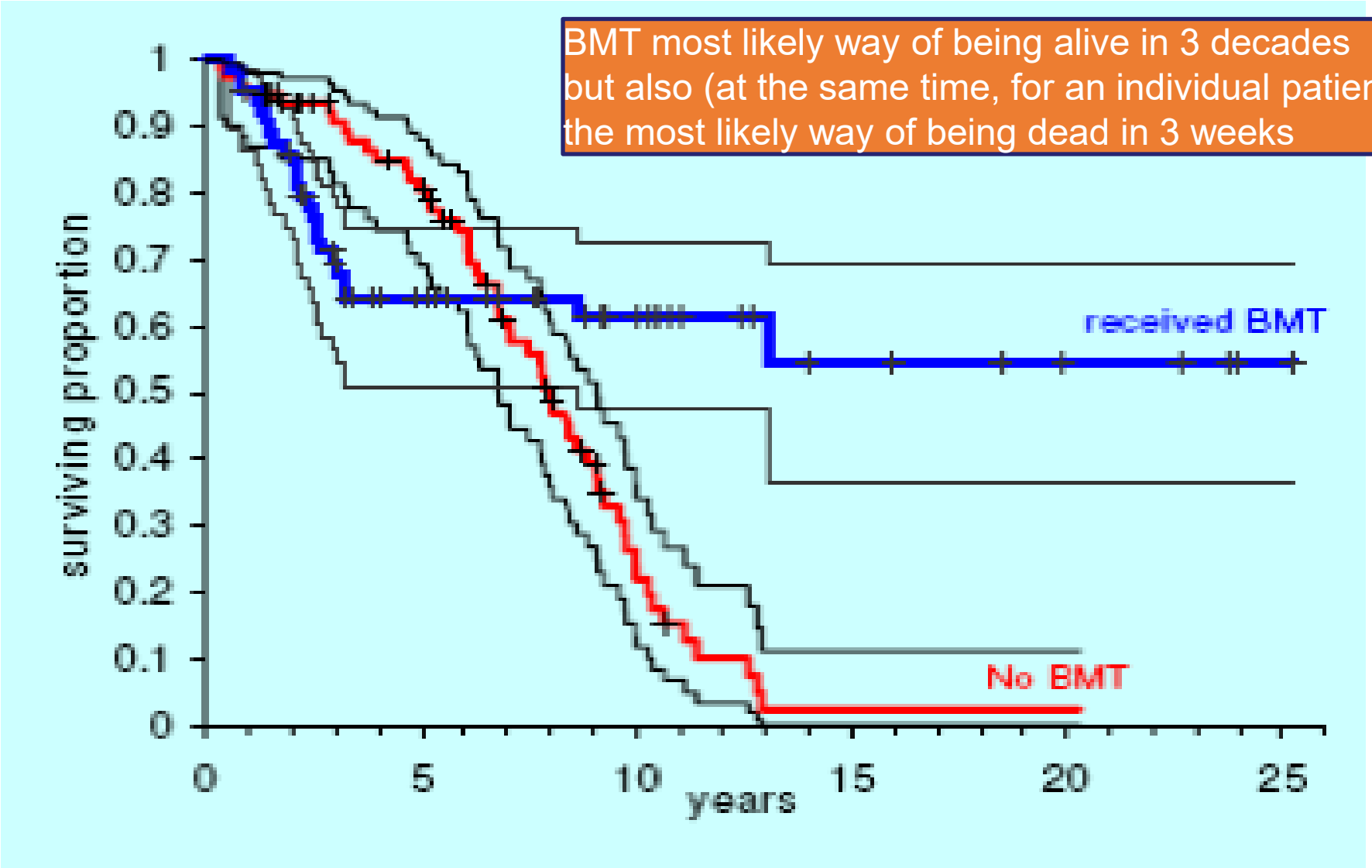


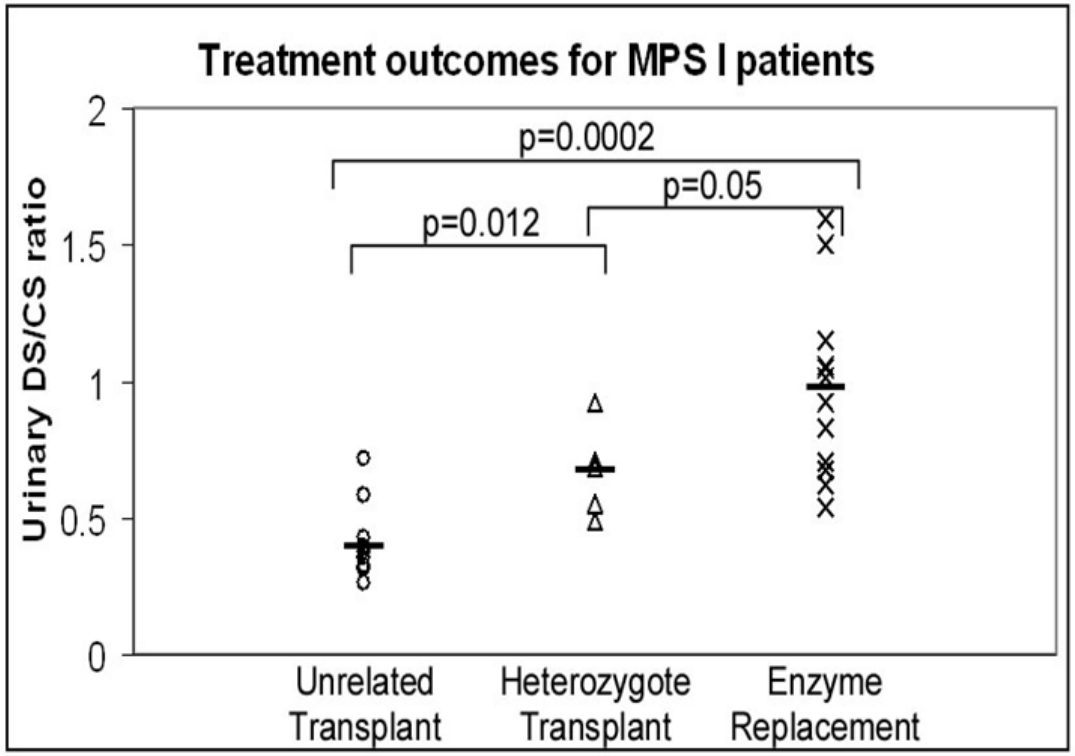
Figure 7a
This patient has undergone HSCT from a normal donor and has fully engrafted (100% donor). Iduronidase activity shows natural fluctuation within the normal range. Residual GAGs have fallen in the initial 6 months post transplant, reaching a plateau that shows a DS/CS ratio consistently <0.5. These data are typical of patients showing full engraftment from normal donors.

Successful SCT influences long term survival of HS patient (n=196)



Haemopoietic system delivering a (transgene) protein in a multisystem fashion …

what other proteins might it be able to deliver?



(Wynn et al, J Peds, 2009)

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Enzyme Delivery
(following cell – transplant – therapy)

- Gene copy number (wild type vs carrier in Hurler)
- Gene expression (Promoter)
- Secretion from cell

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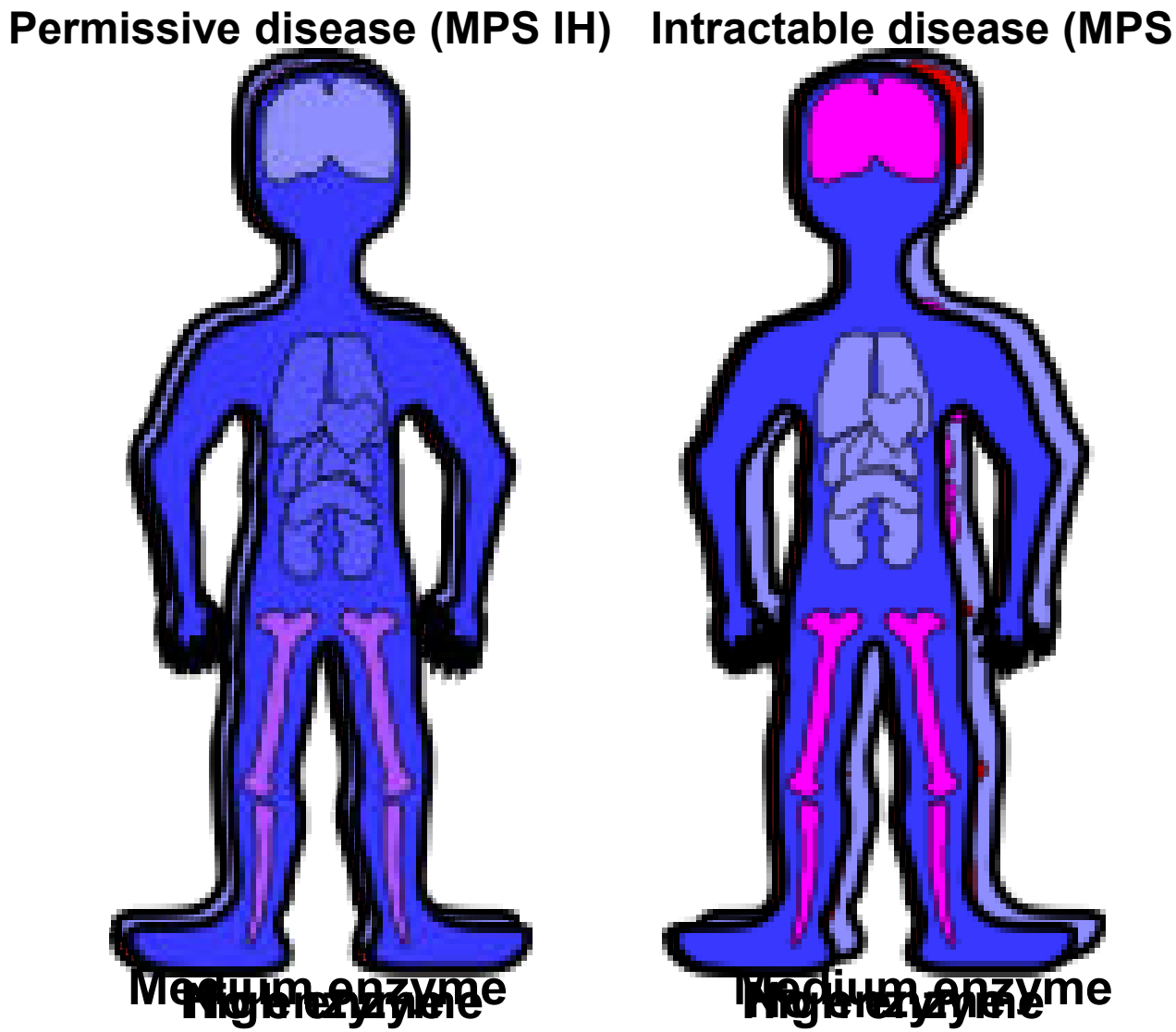
What's the problem? Why is HSCT variable in LSDs; Cells or Enzyme Dose?



Prasad 2008 Blood 112:2979-89

Mucopolysaccharidosis IIIA

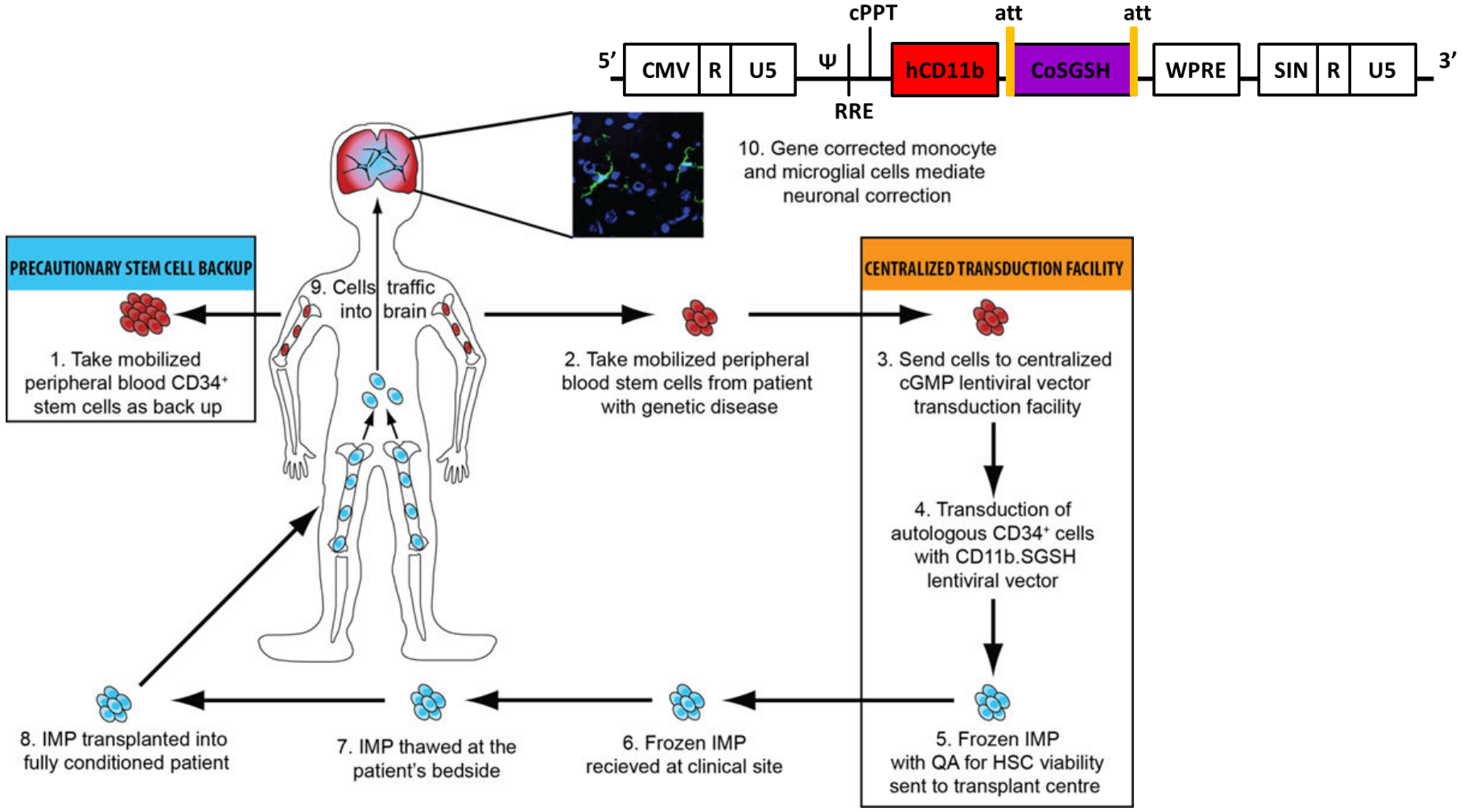
- MPS III (Sanfilippo) describes 4 clinically similar neurodegenerative, lysosomal storage diseases
- MPSIIIA caused by mutations in the *SGSH* gene
- Partially degraded heparan sulphate (HS) glycosaminoglycans (GAGs) accumulate in lysosomes and ECM
- HS accumulation results in lysosomal swelling, secondary storage and cellular dysfunction
- The disease affects children in early life, with progressive cognitive and later motor decline, behavioural problems, hyperactivity and ultimately death in their mid teens
- Enzyme can cross-correct cells – but cannot cross BBB

Speech Age ± SD (yrs)	**Cognitive Function** Age ± SD (yrs)	**Motor Function** Age ± SD (yrs)
Impairment of speech **2.8 ± 1.9** Speech difficult to understand **5.7 ± 2.7** Loss of speech **8.2 ± 3.7**	Deterioration of cognitive function **3.0 ± 1.4** Loss of interest in environment **8.2 ± 3.7** Unresponsiveness **13.1 ± 4.2**	Clumsy walking **4.1 ± 3.6** Aided walking **9.9 ± 4.3** Wheel chair/immobile **12.4 ± 5.3**

National MPS Society
www.mpssociety.org

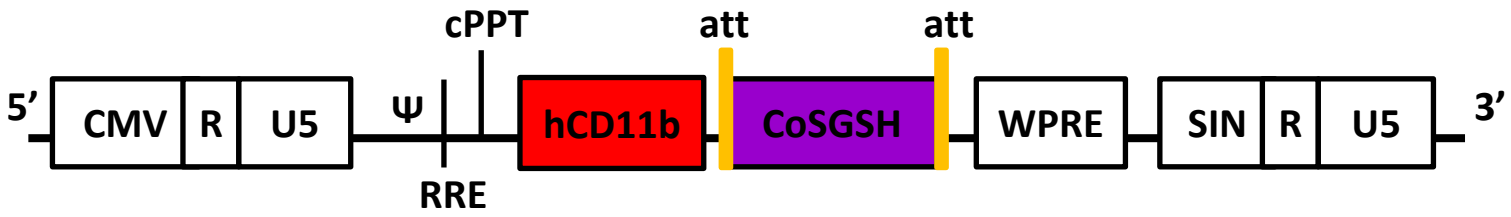
Trial outline for LV-HSC Gene Therapy in MPS IIIA

- Clinical trial outline for MPSIIIA – Cryopreserved IMP with transduction enhancers



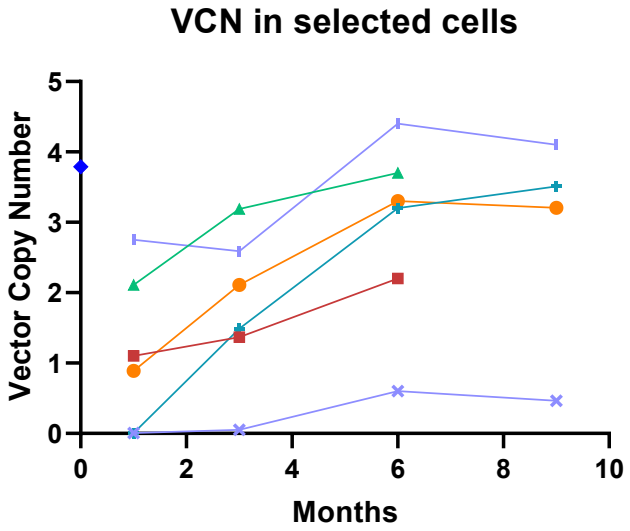
Bigger and Wynn Discovery Medicine April 2014

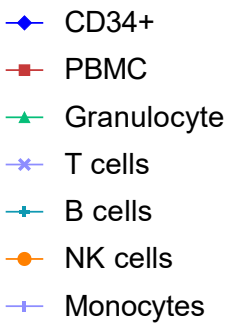
MPSIIIA patient transplanted with CD34+ cells transduced with CD11b.SGSH LV

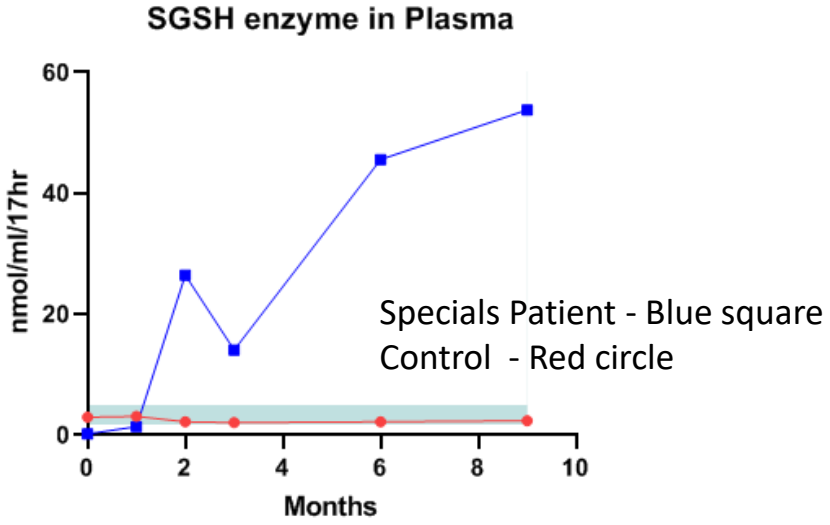


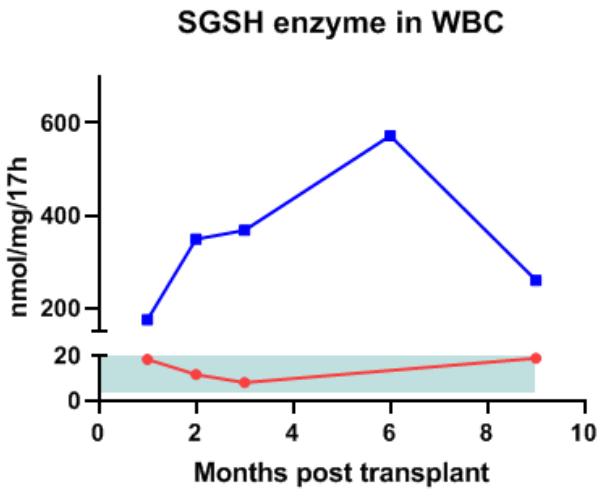
- 2.5 yr old male MPSIIIA patient treated at RMCH by Rob Wynn (Specials)
- Apheresis RMCH 13-18 Dec 2018
- Product Manufacture GOSH/UCL18-20 Dec 2018
- Special product release and shipping to RMCH -18 Jan 2019
- VCN 3.79 (d7), 84% viability, SGSH 4.94 uM 4MU/ug/17h (24 fold normal)
- 5 days full intensity busulfan - target cumulative AUC 90mg/L/h 22-27Jan
- Infused with13x10e6 CD34+ cells/kg at VCN of 3.79 -28 Jan 2019
- Neutrophil engraftment (ANC>500/mm^3) -16 days
- Platelet engraftment (>20,000/mm^3)-39 days

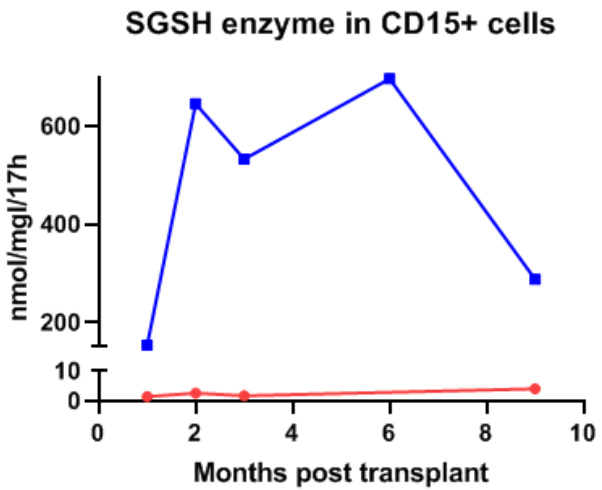
Enzyme and VCN

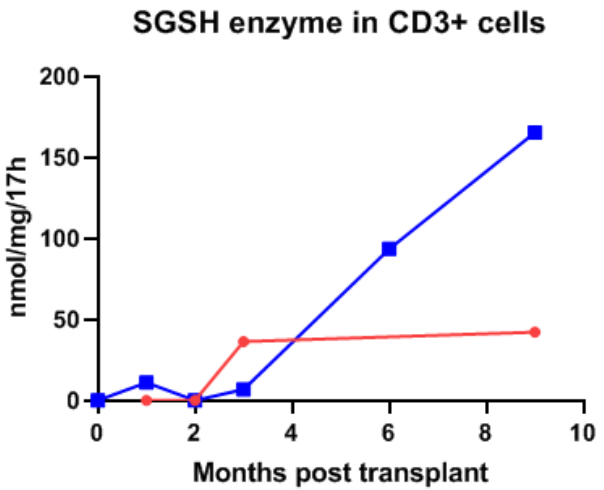








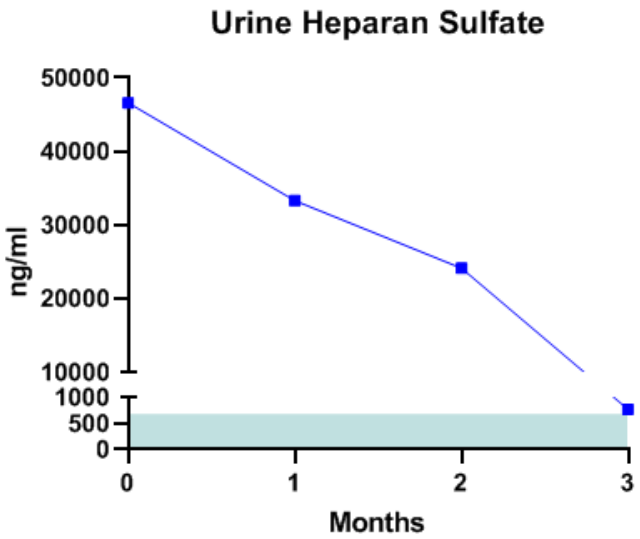




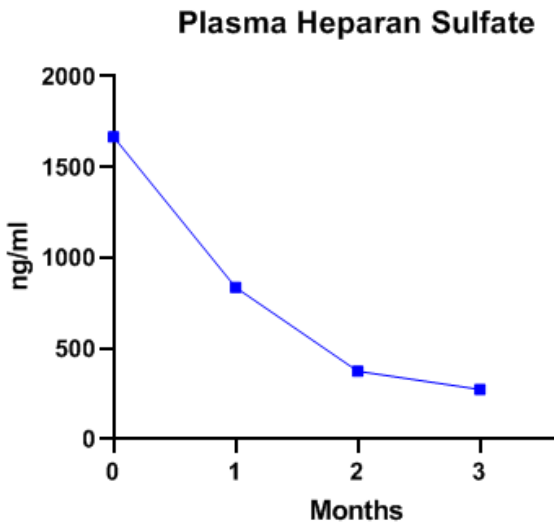
- VCN has stabilised close to input value of 3.79
- Plasma enzyme 11 fold upper limit of normal, WBC enzyme 13 fold normal, CD15 100-300 fold normal,
- CD3 enzyme rises as T cell chimerism increases

Primary Storage

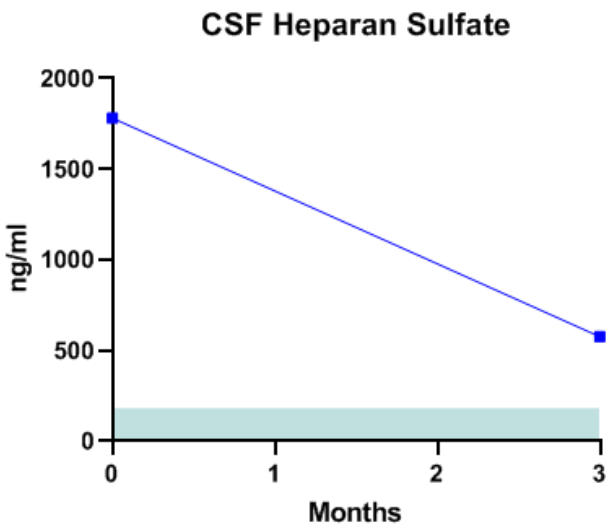
Specials Patient - Blue square



Urine HS reduced by 98% at 3 mo



Plasma HS reduced by 84% at 3 mo



CSF HS reduced by 68% at 3 mo

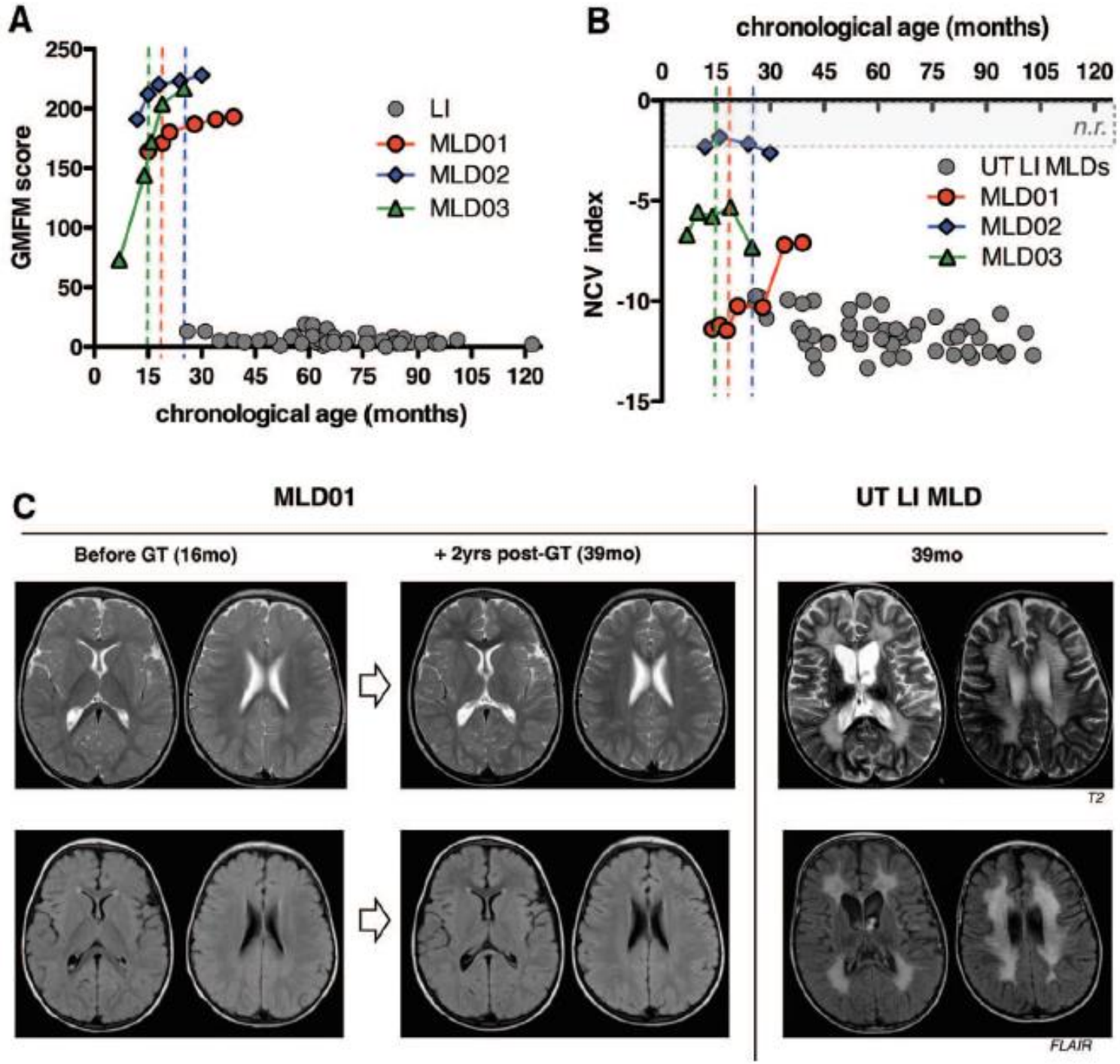
- Urine GAG reduced by 98% after 3 months
- Plasma and CSF HS levels both reduced significantly within 3 months

Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy

Alessandra Biffi,* Eugenio Montini, Laura Lorioli, Martina Cesani, Francesca Fumagalli, Tiziana Plati, Cristina Baldoli, Sabata Martino, Andrea Calabria, Sabrina Canale, Fabrizio Benedicenti, Giuliana Vallanti, Luca Biasco, Simone Leo, Nabil Kabbara, Gianluigi Zanetti, William B. Rizzo, Nalini A. L. Mehta, Maria Pia Cicalese, Miriam Casiraghi, Jaap J. Boelens, Ubaldo Del Carro, David J. Dow, Manfred Schmidt, Andrea Assanelli, Victor Neduva, Clelia Di Serio, Elia Stupka, Jason Gardner, Christof von Kalle, Claudio Bordignon, Fabio Ciceri, Attilio Rovelli, Maria Grazia Roncarolo, Alessandro Aiuti, Maria Sessa, Luigi Naldini*

23 AUGUST 2013 VOL 341 **SCIENCE**

Published by AAAS


A
GMFM score
250
200
150
100
50
0
0 15 30 45 60 75 90 105 120
chronological age (months)
LI
MLD01
MLD02
MLD03
B
chronological age (months)
0 15 30 45 60 75 90 105 120
n.r.
NCV index
0
-5
-10
-15
UT LI MLDs
MLD01
MLD02
MLD03
C
MLD01
UT LI MLD
Before GT (16mo)
+ 2yrs post-GT (39mo)
39mo
T2
FLAIR

AAV

- Non pathogenic virus, different serotypes
- Non-integrating
- Therefore use is restricted to non-mitotic tissue (otherwise cell insertion would be diluted through cell division)
- Immune response to capsid, and retreatment difficult

- EYE (Leber’s congenital amaurosis)(AAV2)
- LIVER (e.g. haemophilia)
- CNS (e.g. SMA)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

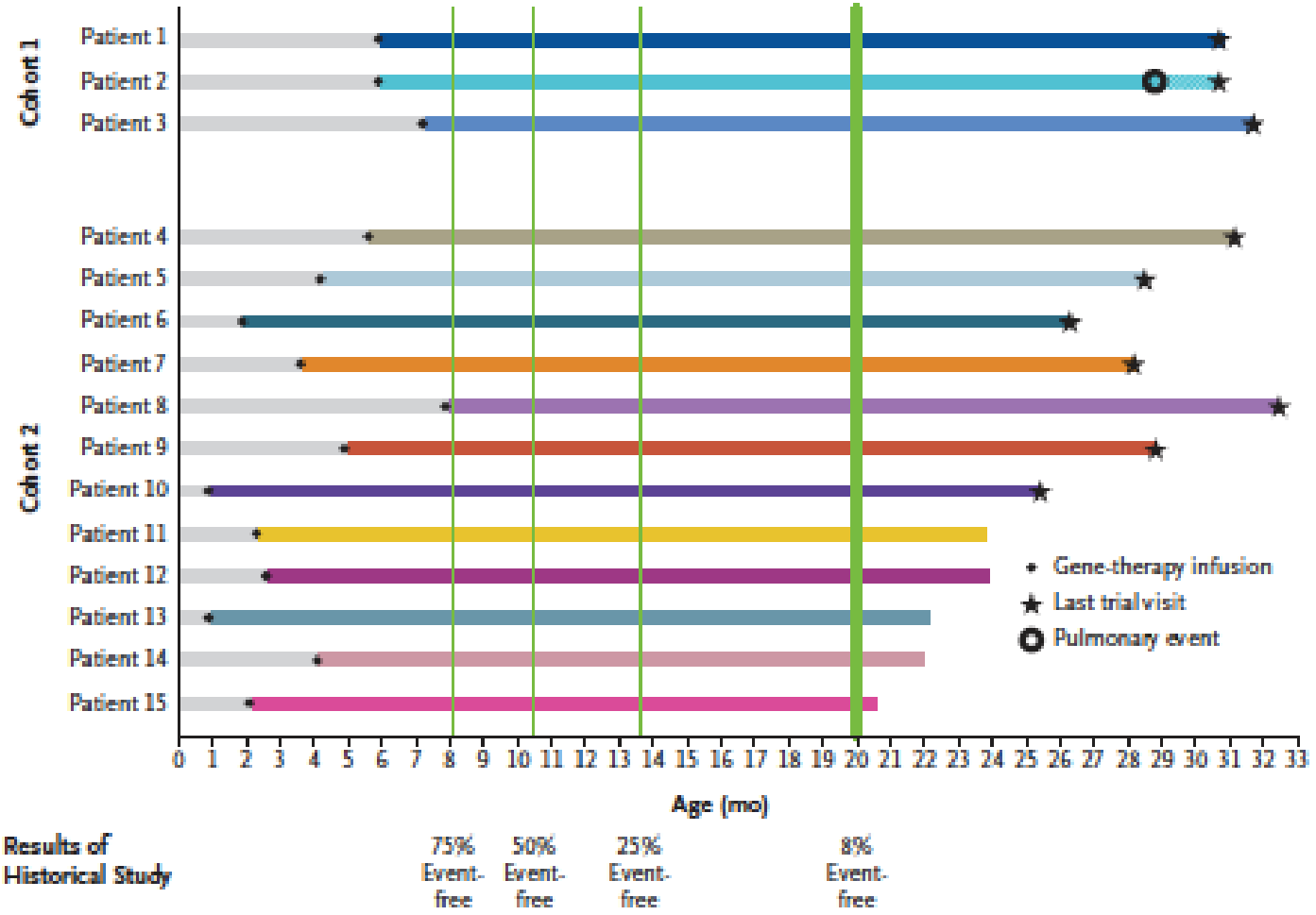


Figure 1. Survival Free from Permanent Ventilation in the 15 Study Patients.

Shown is the duration of survival free from the need for permanent ventilation for the 3 patients in cohort 1, who received a low dose of adeno-associated viral vector containing DNA coding for SMN (6.7×10^{13} vg per kilogram), and the 12 patients in cohort 2, who received a high dose (2.0×10^{14} vg per kilogram). Stars indicate the completion of the ongoing 2-year safety follow-up. The percentages of patients who were event-free in a historical study of spinal muscular atrophy conducted by the Pediatric Neuromuscular Clinical Research Network[4] are provided at the bottom of the graph for a control comparison, as indicated by the vertical green lines. The thicker vertical line indicates the benchmark of 20 months, at which time only 8% of the patients with this disease typically survive without permanent ventilation.

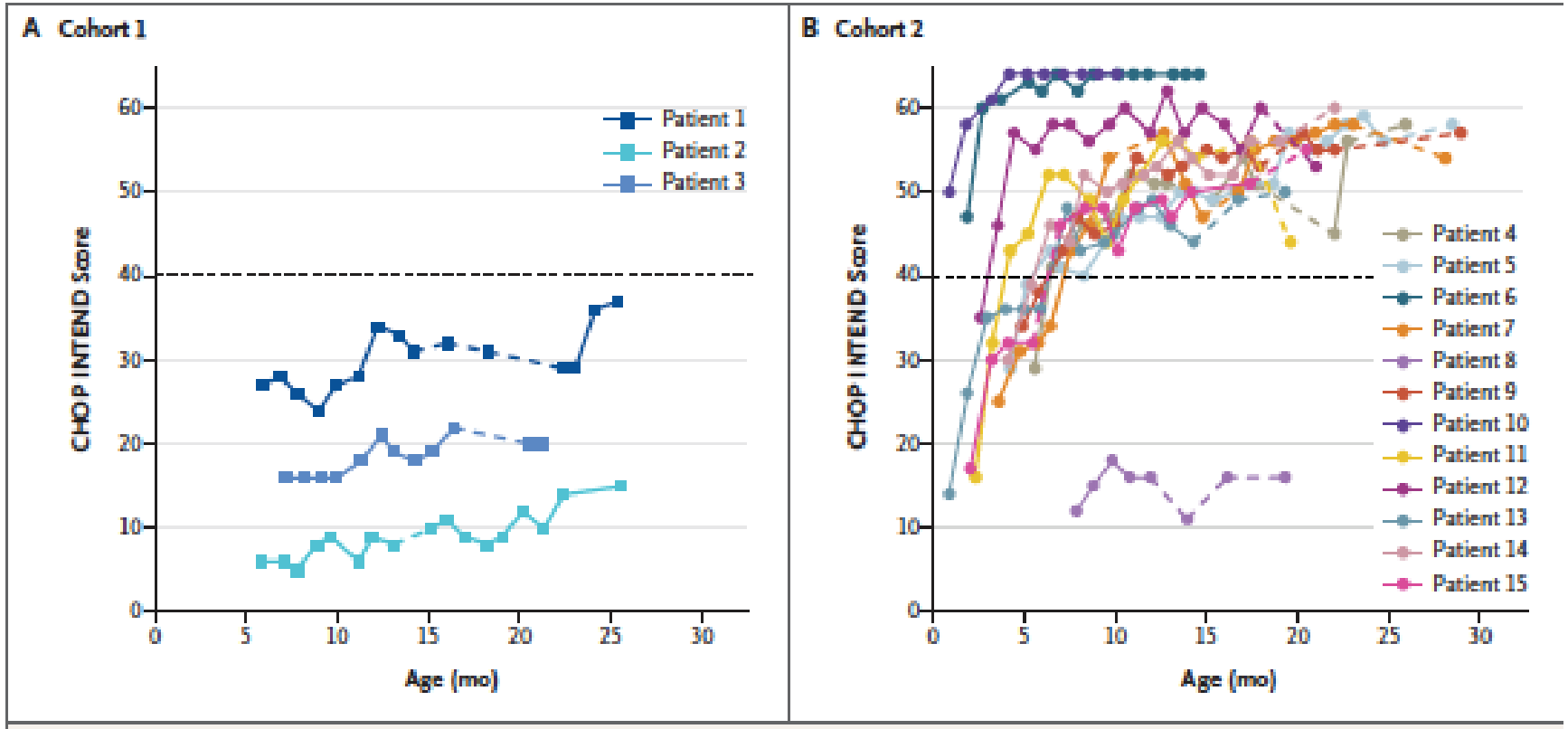


Figure 2. Motor Function after Gene Therapy.

Shown are changes in the score for motor function on the CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale among the 3 patients in cohort 1 (Panel A) and the 12 patients in cohort 2 (Panel B) who received gene therapy with adeno-associated viral vector containing DNA coding for SMN. The scale ranges from 0 to 64, with higher scores indicating better motor function; historical controls with spinal muscular atrophy type 1 never reach 40 points (indicated by the black dashed line). The dashed lines on the individual patient curves indicate either a missed assessment or a partial assessment because of illness, lack of cooperation, or fatigue of the patient; such data were not included in the analyses. The timing of the administration of gene therapy in Figure 1 can be matched with the data shown here for each patient.

This article is more than **11 months old**

The $2m drug reveals medical research as a casino culture

Kenan Malik

Does Zolgensma, a revolutionary one-off treatment for spinal muscular atrophy, really need to cost so much?

Sun 26 May 2019 06.00 BST

How much is a life worth? $2.15m? That's the staggering price of a drug produced by the pharmaceutical giant Novartis that has just come on the market. Zolgensma is a one-off gene therapy treatment for spinal muscular atrophy (SMA), a rare degenerative disorder. Infants with the most severe form usually die within two years. For parents of babies born with SMA, any price is worth paying to save the child's life. Novartis argues that spread across a lifetime, $2.15m is "cost-effective".

It points out, too, the expense of developing such innovative drugs. In this case, though, Novartis did not develop Zolgensma but bought up, for £8.7bn, AveXis Inc, the company that did. The *Wall Street Journal* described the acquisition as a "bet". The price of Zolgensma is the return necessary for that gamble to be successful.

- **Metabolic SC GT programme**
- CAR-T and cancer gene therapy programme
- MSC and inflammatory disease, and metabolic bone disease gene therapy programme

Indications

- MALIGNANT (HAEMATOLOGICAL) DISEASE
- NON-MALIGNANT HAEMATOLOGICAL (Gene therapy in most cases!)

(Disorder of stem cell number or function, or number or function of their mature progeny)

- NON-MALIGNANT, NON-HAEMATOLOGICAL (Gene therapy!)

(METABOLIC DISEASES)

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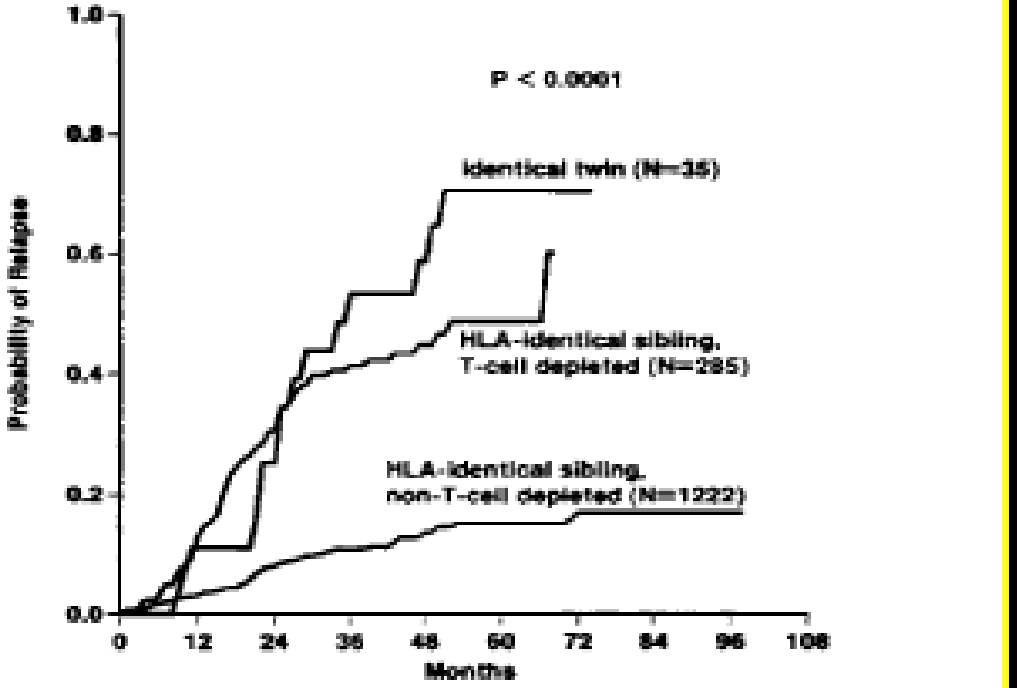
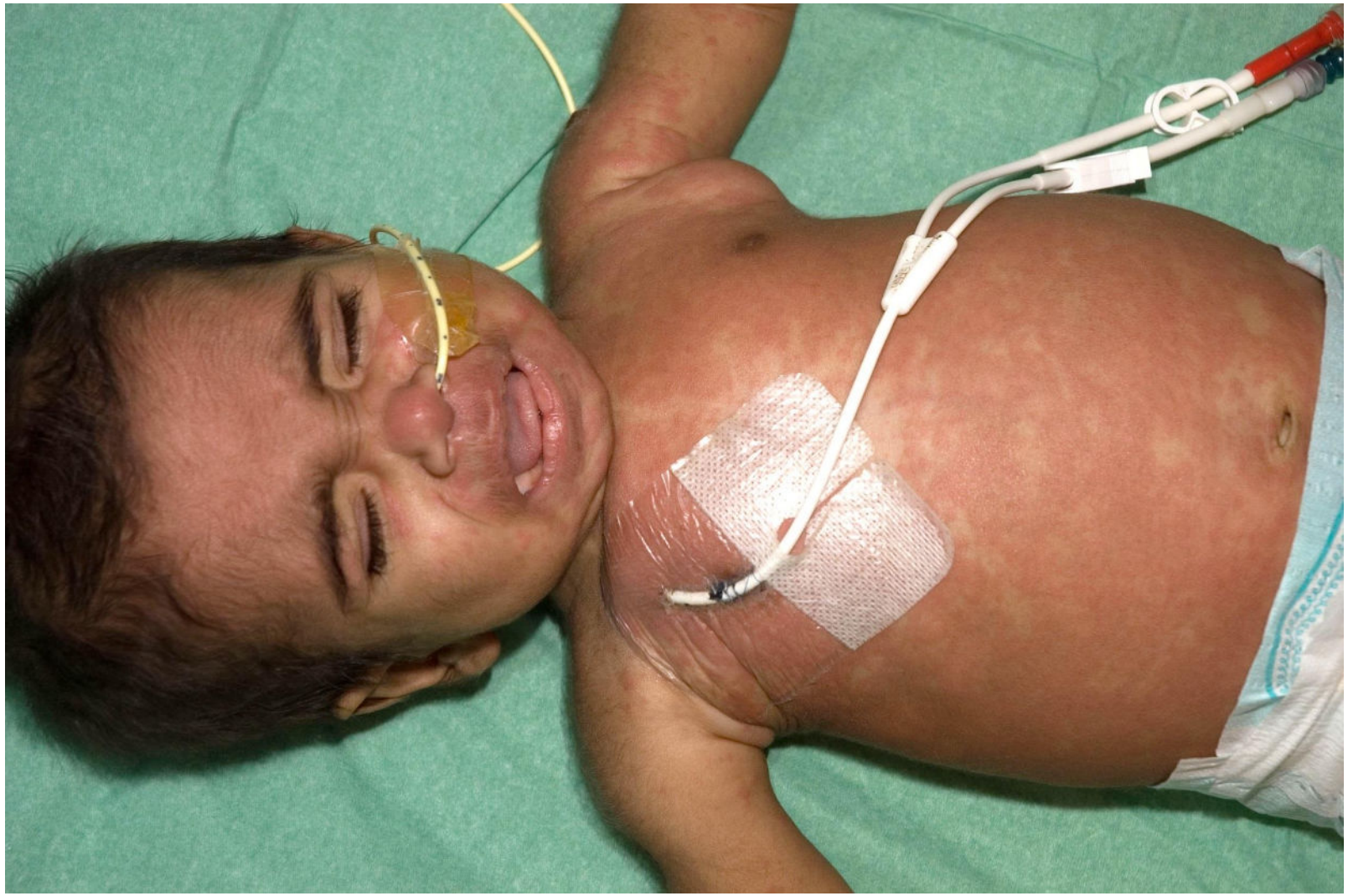
The University of Manchester

Graft-versus-Leukemia Effect



Central Manchester University Hospitals NHS
NHS Foundation Trust

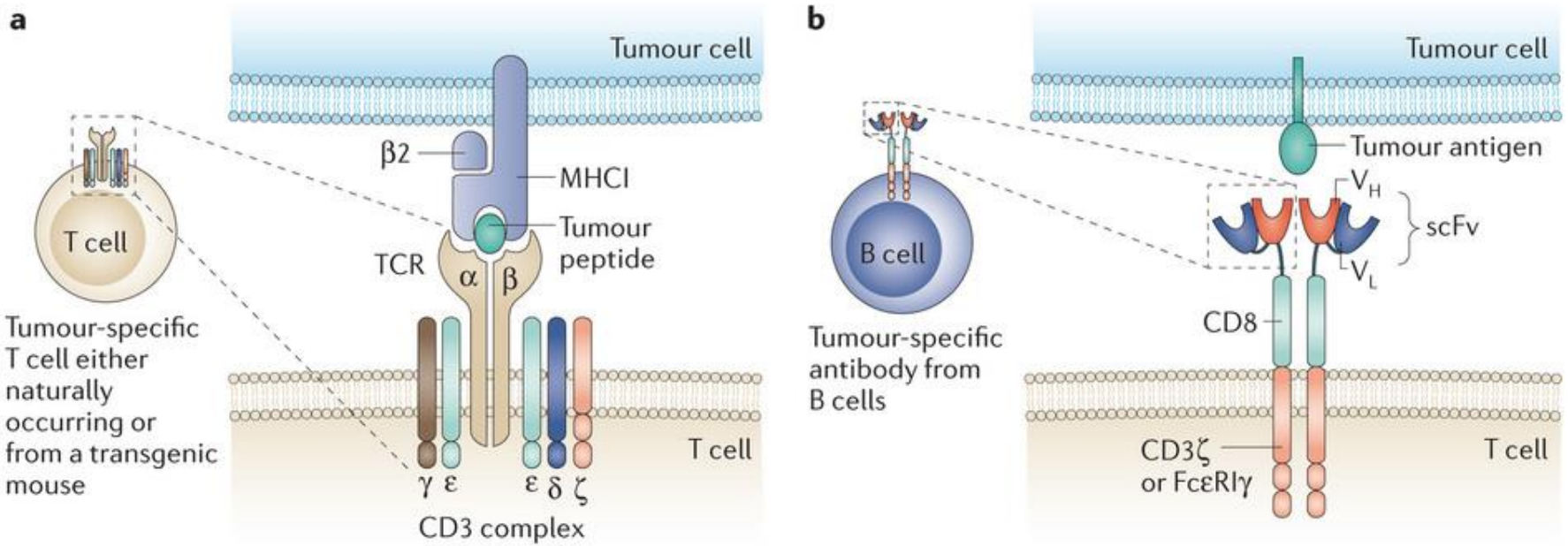


Graft versus Leukaemia, Manchester strategies

- Transplant as a platform for immune therapies in leukaemia
- JMML, AML, T-ALL more than B-ALL

- Optimising GvL

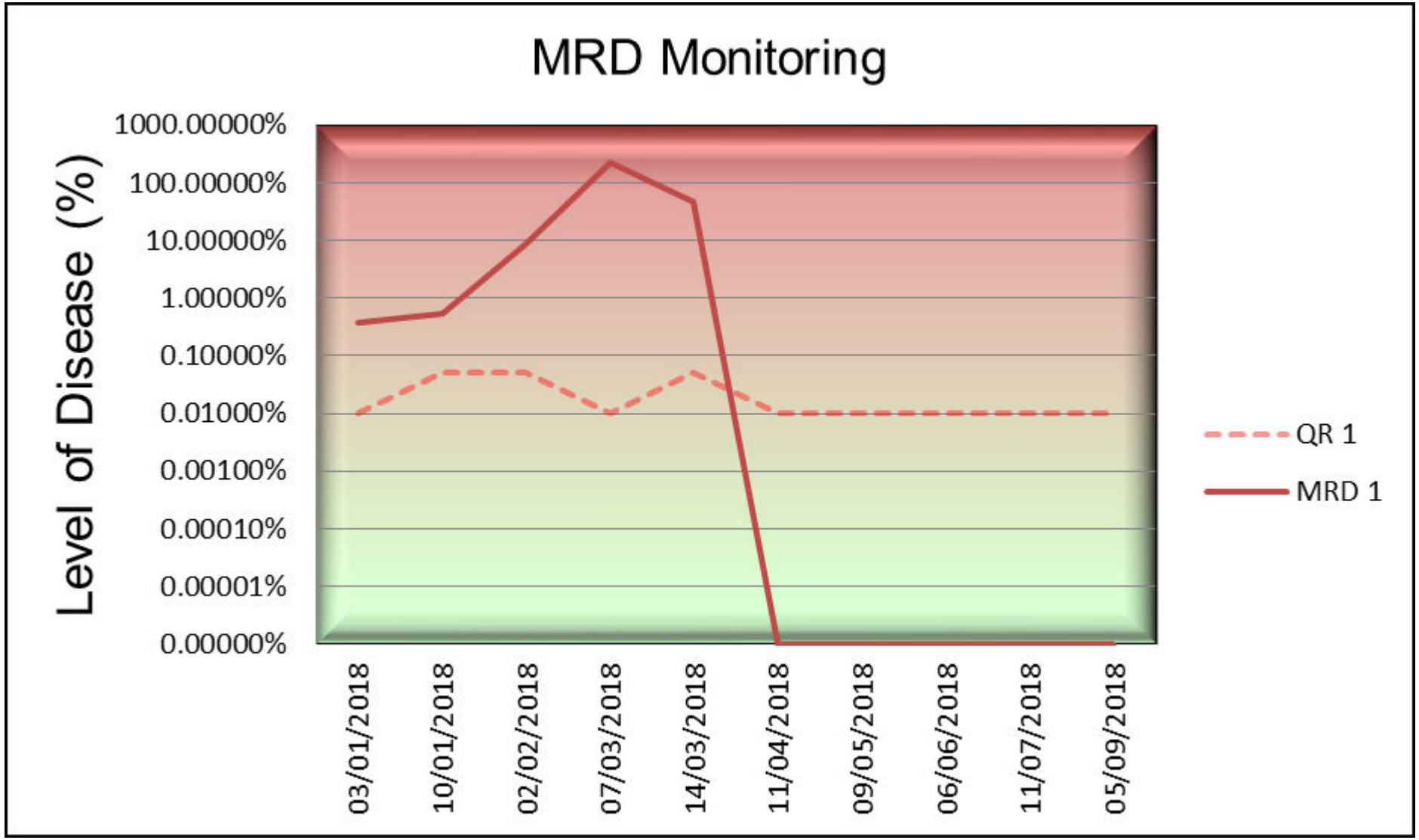
- Using cord blood (granulocytes?) and choosing mismatch
- T-replete grafts
- Donor Lymphocyte Infusions where mixed T-cell chimerism

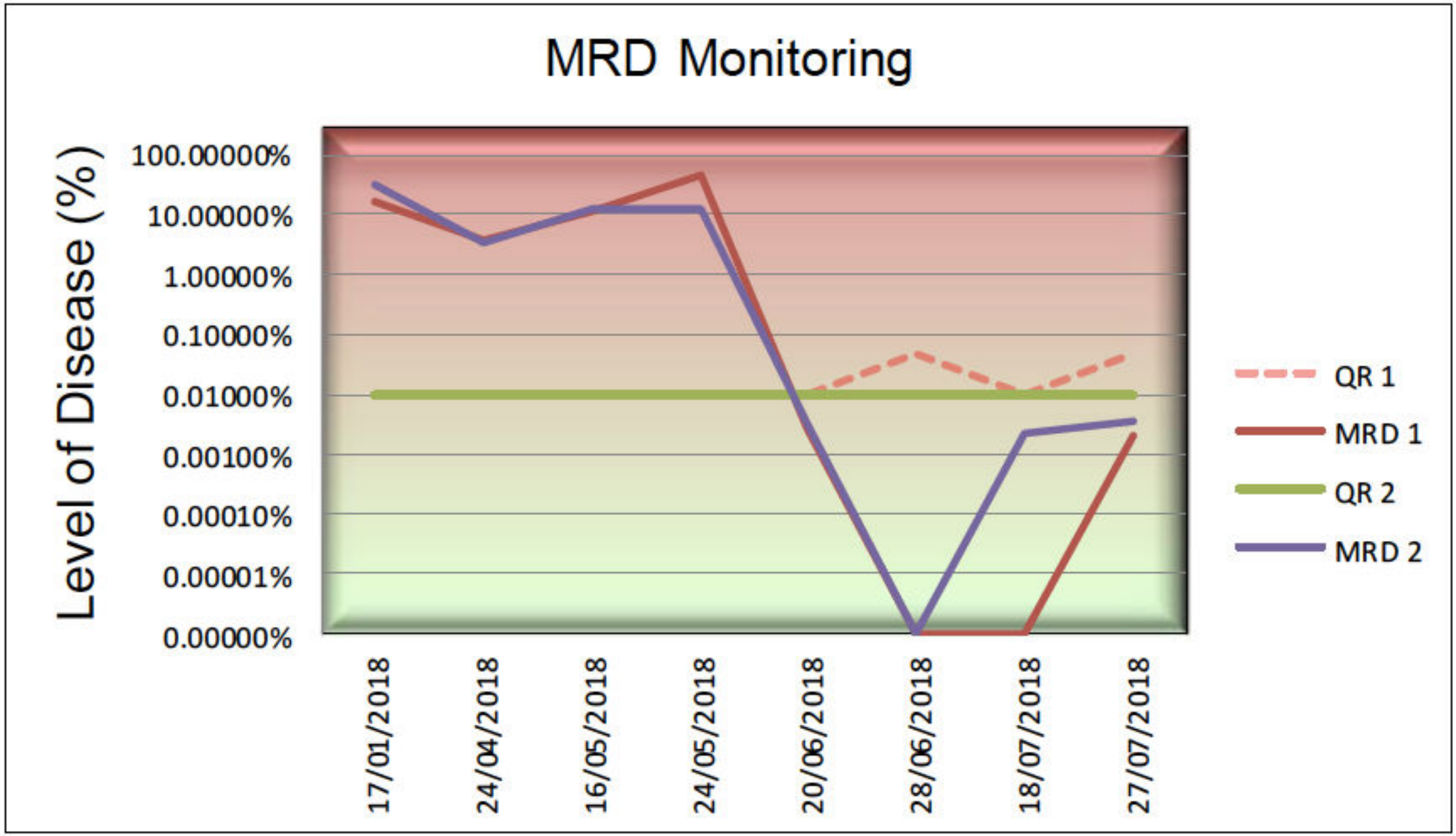


Nature Reviews | Cancer

Toxicities

- Of leucapheresis, taking T-cells,
- Of lymphodepletion
- Of infusion, a cryopreserved stem cell product
- CRS, expanding, activated T-cells – we have not seen beyond grade 2 in Manchester, so none to ICU, no inotrope support (related to tumour burden)
- Reverse with tocilizumab, anti-IL6
- Neurology
- B cell aplasia, and need for IVIG


MRD Monitoring
Level of Disease (%)
1000.00000%
100.00000%
10.00000%
1.00000%
0.10000%
0.01000%
0.00100%
0.00010%
0.00001%
0.00000%
03/01/2018
10/01/2018
02/02/2018
07/03/2018
14/03/2018
11/04/2018
09/05/2018
06/06/2018
11/07/2018
05/09/2018
QR 1
MRD 1


MRD Monitoring
Level of Disease (%)
100.00000%
10.00000%
1.00000%
0.10000%
0.01000%
0.00100%
0.00010%
0.00001%
0.00000%
17/01/2018
24/04/2018
16/05/2018
24/05/2018
20/06/2018
28/06/2018
18/07/2018
27/07/2018
QR 1
MRD 1
QR 2
MRD 2

Relapse after CAR-T

- Loss of target antigen expression
- Evolution of leukaemia with loss of target antigen expression
- Particularly described in MLL leukaemia

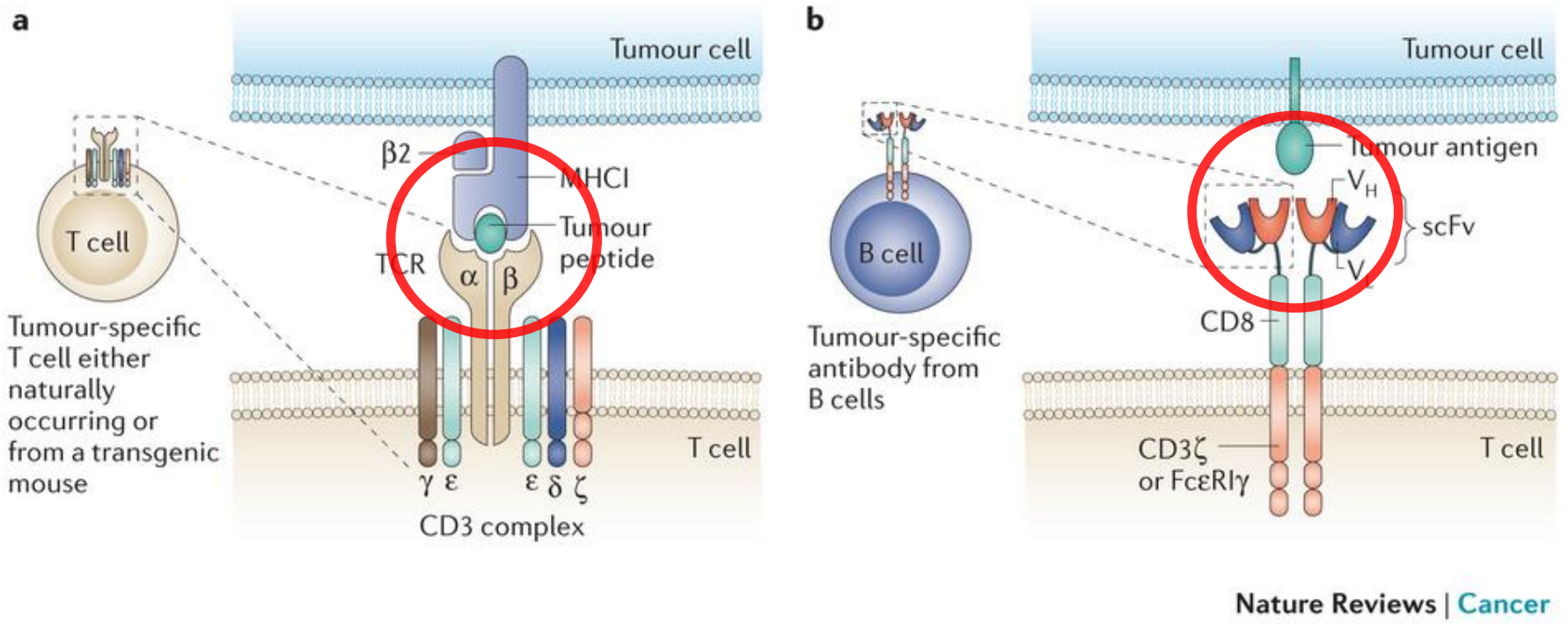
- Loss of CAR-T

Role of CAR-T?

- Bridge to transplant, Final therapy?
- Non-lymphoid leukaemias (targets)

Future of CAR-T cell therapies

- Combination with checkpoint inhibitors
- Turn on, turn off, incorporation of suicide genes
- Beyond ALL, into solid tumours
    - ❖Getting the T-cell into the tumour
    - ❖Antigen selection
    - ❖An immune suppressant tumour microenvironment
- Identification of antigens specific to solid tumours (to reduce on-target, off tumour toxcity … B-cell aplasia is ok, can manage)



Intracellular antigen, expressed at cell surface,
By class I

Bespoke TCR gene therapy – individual as HLA-specific

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Summary of Talk

- Role of transplant, its utility, its imitations and therefore our future direction in:
  - ➢ Childhood cancer (Allo transplant to CAR, and back?)
  - ➢ Genetic illnesses (PID, Haematology, Metabolic, and beyond?)

Central Manchester University Hospitals NHS
NHS Foundation Trust

BMT, MANCHESTER CHILDREN'S HOSPITAL

BMT, Denise Bonney, Prashant Hiwarkar, Helen Campbell,
Helametha Doss,
FELLOWS, and RESEARCH FELLOWS
PHARMACY, Tas Khalid and team
STEM CELL Wendy Ogden and Lab
TRANSPLANT Kay Poulton and Lab
NURSES, WARD, EVERYONE

NATIONAL and INTERNATIONAL

Simon Jones, Manchester, Paul Veys, London
Rod Skinner, Newcastle
Jaap Jan Boelens, MSK
Paul Orchard, Minnesota
Caroline Lindemans, Utrecht
Maria Ester Bernardo, Milan
Arjan Lankaster, Leiden

LABORATORY

Brian Bigger, Manchester, and team

Professor Ed Wraith, RMCH

Central Manchester University Hospitals NHS
NHS Foundation Trust

Q&A

Please add any question you have into the Q&A box

Please fill in feedback survey, your input is really valuable to us

Upcoming webinars,

Covid vaccines and ATMP likeness, 25th May at 3pm,

Peter Openshaw, *Professor of Experimental Medicine, Imperial College London*

ATMP treatments for diabetes, 10th June at 4pm,

James Shaw, *Professor of Regenerative Medicine for Diabetes, Newcastle University*

https://www.theattcnetwork.co.uk/network/advanced-therapy-education-webinar-series