Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Improving outcomes for children with leukaemia internationally: the results of scientifically designed clinical trials and translational research

1. Summary of the impact

Researchers at the University of Manchester (UoM) have made a significant impact nationally and internationally on improving the outcome for children with acute lymphoblastic leukaemia (ALL) (~450 pa in the UK). The changes in clinical practice based on our research are now national standards of care for children with *de novo* and relapsed ALL in the UK and Ireland. Other international groups have adopted key findings from the results of our frontline trials. Our relapse protocol for childhood ALL underpins European and North American strategy for the management of relapsed disease.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Key UoM researchers:

- **Tim Eden** (Professor of Paediatric Oncology, 1994-2007; Honorary Professor 2007- date)
- **Vaskar Saha** (Professor of Paediatric Oncology, 2006 - date)

UoM is recognised both nationally and internationally as a centre for expertise in Teenage and Young Adult Cancers and nationally as a centre for clinical studies in childhood leukaemia. The UK chair in Teenage and Young Adult Cancer (funded by the Teenage Cancer Trust) is based here (**Eden**, 2005-2011; **Radford,** 2010-date) and Manchester is the sponsor and clinical trial centre for two national phase III clinical trials in childhood ALL.

Eden was chief investigator for the two main path-changing protocols in childhood ALL in the UK, namely UKALL VIII and ALL97/99 (1). The latter trial was the first to stratify patients for risk in the UK based on the early response to therapy (2), leading to an improvement in outcome of high-risk patients. His work in the period 1993-2003 led to the routine use of dexamethasone (instead of prednisolone), mercaptopurine (instead of thioguanine) and pegylated L-Asparaginase (PEG-Asnase) instead of native asparaginase in childhood ALL in the UK and elsewhere. These drugs are now the mainstay in the therapy of childhood ALL in UK and Ireland.

Incorporating the three drugs identified by **Eden**'s work, **Saha** developed a new concept for the treatment of relapsed ALL for all patients being treated in UK and Ireland (3). The trial introduced minimal residual disease (MRD) based risk stratification to select for patients to either receive chemotherapy or an allogeneic transplantation and was the first randomised international trial for relapsed ALL. A bespoke remote entry clinical trial management system was constructed indigenously. This system permitted remote registration and data entry, provided decision support and standardised the reporting of MRD across all recruiting centres. This approach allowed countries including the Netherlands, Australia and New Zealand to adapt the study rapidly for their patients at all centres. This clinical study, the ALLR3 trial (2003-2013), forms the basis of relapse strategies in childhood ALL worldwide. A centralised cell bank for the UK was developed in Manchester for this trial. Building translational research into clinical trials has also allowed the identification of previously unidentified mechanisms of therapeutic failure paving the way for novel therapeutic strategies (4).

Eden and **Saha** participated in and led international initiatives in childhood ALL. They represent the UK on the influential international think-tank (the Ponte de Ligno group). As ALL is a rare disease and associated with a high cure rate, the numbers of patients at a risk of relapse (or relapsing) are small in any study group. Thus international collaborative studies are key to

identifying optimal strategies for these sub-groups.

An example is EsPhALL, the only randomised study of tyrosine kinase inhibitors in Philadelphia-positive (Ph+) ALL (2004-to date) (5), which is a European collaborative study. Ph+ ALL is a high-risk group of childhood ALL and almost all patients are transplanted in first remission. **Saha** helped design the study and analyse the randomised data, with the UK contributing the maximum number of randomised patients. Another large international study to which **Saha** contributed to design and writing identified a therapeutic strategy for patients who fail initial therapy (6).

3. References to the research

1. Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, **Eden T**. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *British Journal of Haematology*. 2005;129:734-745. DOI: 10.1111/j.1365-2141.2005.05509.x

2. Mitchell C, Payne J, Wade R, Vora A, Kinsey S, Richards S, **Eden T**. The impact of risk stratification by early bone-marrow response in childhood lymphoblastic leukaemia: results from the United Kingdom Medical Research Council trial ALL97 and ALL97/99. *British Journal of Haematology*. 2009;46:424-36. DOI: 10.1111/j.1365-2141.2009.07769.x

3. Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV, Ancliff P, Morgan M, Masurekar A, Goulden N, Green N, Revesz T, Darbyshire P, Love S, **Saha V**. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*. 2010;376:2009-17. DOI: 10.1016/S0140-6736(10)62002-8

4. Patel N, Krishnan S, Offman MN, Krol M, Moss CX, Leighton C, van Delft FW, Holland M, Liu J, Alexander S, Dempsey C, Ariffin H, Essink M, **Eden TO**, Watts C, Bates PA, **Saha V**. A dyad of lymphoblastic lysosomal cysteine proteases degrades the antileukemic drug L-asparaginase. *The Journal of Clinical Investigation*. 2009;119:1964-73. DOI: 10.1172/JCI37977

5. Biondi A, Schrappe M, De Lorenzo P, Castor A, Lucchini G, Gandemer V, Pieters R, Stary J, Escherich G, Campbell M, Li CK, Vora A, Arico M, Rottgers S, **Saha V**, Valsecchi MG. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncology*. 2012;13:936-45. DOI: 10.1016/S1470-2045(12)70377-7

6. Schrappe M, Hunger SP, Pui CH, **Saha V**, Gaynon PS, Baruchel A, Conter V, Otten J, Ohara A, Versluys AB, Escherich G, Heyman M, Silverman LB, Horibe K, Mann G, Camitta BM, Harbott J, Riehm H, Richards S, Devidas M, Zimmermann M. Outcomes after Induction Failure in Childhood Acute Lymphoblastic Leukemia. *The New England Journal of Medicine*. 2012; 366:1371-81. DOI: 10.1056/NEJMoa1110169

Key funding underpinning the research

Cancer Research UK: Clinical and Biological Studies in Acute Leukaemias of Childhood. 01/10/2006 – 30/09/2013, Total Award: £2,855,485 to **Saha**.

Teenage Cancer Trust: Chair of Teenage Cancer Trust. 01/10/2005 – 30/09/2015, Total Award: £2,500,000 to **Eden**.

Cancer Research UK: Professor Vaskar Saha Personal Support 01/09/2006 – 31/08/2009 Total Award: £405,936 to **Saha**.

Leukaemia & Lymphoma Research: Molecular Pharmacology of Imatinib in Patients with Philadelphia Positive ALL. 01/10/2006 – 28/02/2011. Total Award: £170,215 to **Saha**.

Leukaemia & Lymphoma Research: Correlation of AEP expression with Asparaginase activity, hypersensitivity and antibody formation in acute lymphoblastic leukaemia (ALL) of childhood. 01/12/2008 – 22/03/2013.Total Award: £265,800 to **Saha**.

European Commission (FP7): International study for treatment of childhood relapsed ALL 2010 with standard therapy, systematic integration of new agents, and establishment of standardized diagnostic and research. 01/10/2011 – 30/09/2016. Total Award: £430,724.

4. Details of the impact

See section 5 for corroborating sources S1-S6.

Context

Children with ALL in the UK (~450 pa) now benefit from one of the highest cure rates in the world. During 1980-2000, however, UK success rates fell below other international groups. At that time it was unclear as to why this was the case and both **Eden** and **Saha** were instrumental in initiating changes that have turned this around, so that our clinical outcomes in 2013 are among the best in the world. The changes included the introduction of risk stratification using MRD, optimising drug schedules and the testing of drugs hitherto not used widely in children with ALL.

Pathways to impact

Eden's national leadership has been pivotal to the improvement in outcome in children with ALL in UK. In 1999, he introduced risk stratification (2), incorporated modern therapeutic blocks, the use of dexamethasone and PEG-Asparaginase (ALL99) (1), which evolved into the ALL2003 trial. Similarly, between 1990 and 2003, there had been little improvement in outcome in relapsed childhood ALL worldwide. **Saha** used a novel design for a relapse trial in childhood ALL (3) and developed strategies for high risk ALL in collaboration with international groups (5, 6). Based on the observations made in the clinical trials, **Saha** designed translational research to understand the biological mechanisms for the variations in therapeutic response (4) leading to further refinements in therapy now being tested in frontline ALL trials in UK.

Reach and significance of the impact

These clinical trials in childhood ALL have led to an improvement of outcome in children with ALL in the 2008-2013 period in the UK and shaped treatment strategies worldwide. As a result of the changes initiated by **Eden**, in the period of 2008-2013, the survival rates in newly diagnosed childhood ALL in UK are now over 85%, among the best in the world (2).

ALLR3, the trial designed by **Saha** has improved by 10% the outcome for children with relapsed ALL in the UK, Netherlands, Australia and New Zealand and identified a role for the drug Mitoxantrone in childhood ALL (3) (S1-S3). The Vice-Chair for Relapse, ALL Committee, Children's Oncology Group and Professor of Paediatrics at The University of Toronto underlines the importance of these findings: 'the outcomes achieved with the mitoxantrone arm of the R3 regimen, as published in the Lancet Oncology by Parker et al [reference 3 above], represent the best published results to date for the first relapse of childhood ALL. The R3 regimen thus represents a new standard of care for children with first relapse of childhood ALL, and has been adopted as such at a number of leading institutions around the world for children with first relapse of ALL, including my own institution, the Hospital for Sick Children.' (S4, S5) Mitoxantrone improves the outcome of all categories of relapses, compared to the traditionally used Idarubicin. However MRD levels in both arms of the trial were identical, suggesting that the effect of Mitoxantrone is not explained by direct cytotoxicity. Thus MRD cannot be used reliably as a surrogate marker for outcome. The trial shows that MRD levels can be used to identify patients with relapsed ALL who do not need an allogeneic transplant.

The ALLR3 trial design underpins the current international trial in relapsed disease funded by the European Union FP7 programme. This is the largest study of its kind in the world running across 20 different countries (IntReALL, http://www.intreall-fp7.eu/) and incorporates the MRD stratification for transplantation. As chair of the International study group on Relapsed and Resistant Disease in Childhood ALL (I-BFM-SG), Co-Chief Investigator for IntReALL and an advisor to the European Medicines Agency, **Saha** has been able to initiate studies utilising new agents in relapsed childhood ALL by collaborating with industry e.g. IntReALL will use the drug Epratuzamab (ImmunoMedics). The standards of procedures developed for the ALLR3 cell bank now form the basis of an IntReALL cell bank. The ALLR3 cell bank also led to the centralisation of

the UK childhood leukaemia cell bank to Manchester Biobank (funded by LLR).

The EsPhALL study has shown the benefit of a targeted drug (imatinib) in conjunction with conventional chemotherapy, in this high-risk population (5). Moreover the use of imatinib has resulted in a dramatic decrease in MRD levels, and we now only transplant those with high MRD levels. Thus currently imatinib is given to all children with Ph+ ALL in Europe and other countries. Less than half of the children previously transplanted now require one, considerably reducing the burden of therapy. The trial has led to the further development of this group with the inclusion of the Children's Oncology Group (USA). A current collaborative study, between USA, Italy and UK is investigating the role of Dasatinib on the EsPhALL chemotherapy backbone (NCRN 350) (S6). This study is being replaced by a 20-country collaborative effort in 2015.

In the era 1993-2013, Manchester investigators have led the way in setting standards for the improvement of outcome in childhood ALL. During the period 2008-2013, the ensuing research of that period has led to a greater than 10% improvement in the cure of both *de novo* and relapsed ALL. Prompt dissemination of our results has enabled international colleagues to rapidly incorporate the knowledge gained from our trials thus benefitting patients worldwide.

5. Sources to corroborate the impact

S1. The ALLR3 protocol is now the standard of care for children with relapsed ALL in UK, Netherlands, Australia and New Zealand and all patients receive the drug Mitoxantrone. This is also being evaluated by the Children's Oncology Group in the USA (http://www.cancer.gov/cancertopics/pdq/treatment/childALL/HealthProfessional/Page8#Section_1401)

S2. Letter from Senior Paediatric Haematologist-Oncologist, Women's and Children's Hospital, North Adelaide, Australia.

S3. The COG are now using the ALLR3 protocol as a strategy. (http://onlinelibrary.wiley.com/doi/10.1002/pbc.24420/full)

S4. Letter from Vice-Chair for Relapse, ALL Committee, Children's Oncology Group, Director, Garron Family Cancer Centre, The Hospital for Sick Children and Professor of Paediatrics, The University of Toronto, Canada.

S5. Hunger SP, Loh ML, Whitlock JA, Winick NJ, Carroll WL, Devidas M, Raetz EA, Committee COGALL. Children's Oncology Group's 2013 blueprint for research: acute lymphoblastic leukemia. *Pediatric Blood Cancer*. 2013;60(6):957-63. DOI: 10.1002/pbc.24420

S6. NCRN 350 (http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=11289)