Institution: King's College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Improved survival of patients with acute promyelocytic leukaemia due to personalised treatment and early warning of re-occurrence

1. Summary of the impact

Acute promyelocytic leukaemia (APL) is of interest because it is the first cancer that can be cured with drugs that target a unique molecular abnormality. KCL research has developed accurate molecular techniques which are essential to diagnose the disease, guide treatment, and monitor for relapse. Sub-microscopic levels of leukaemic cells remaining in the patient's bone marrow after treatment (referred to as 'minimal residual disease') give an early warning of re-occurrence of the disease. Our laboratory has developed sensitive tests for these cells, allowing treatment to be tailored to individual patient needs. This has had a major impact on APL diagnosis and monitoring and has been incorporated in national and international disease-treatment guidelines.

2. Underpinning research

An aggressive but curable form of leukaemia: APL is one of the commonest forms of acute myeloid leukaemia (AML). It can be particularly aggressive, with a very high risk of fatal bleeding. However it is also highly treatable, being the first type of leukaemia in which molecularly-targeted drugs have been successfully used in clinical practice to substantially improve disease outcomes.

APL is caused by breaks in chromosomes 15 and 17, and a rearrangement (translocation) of genetic material between these chromosomes. This leads to part of the *PML* gene on chromosome 15 becoming fused with part of another gene called *RARA* on chromosome 17. The protein produced from this fusion gene (*PML-RARA*) causes white blood cells to develop abnormally and build up in the bone marrow. However, the protein can be successfully destroyed by targeting it with a drug called ATRA (all-*trans* retinoic acid) and with arsenic trioxide.

KCL staff's long standing research into APL: The foundation for molecular diagnostics and disease monitoring in APL was work carried out by the Solomon laboratory in 1990 (ICRF, London) on the regions where breaks occurred in the chromosomes. Subsequent work on APL diagnostics and monitoring at KCL was carried out by Professor David Grimwade (ICRF, London, 1994-1998; KCL, 1998-present).

KCL research supporting the diagnosis of APL: The KCL research group has investigated the causes of APL, and gained greater insights into the translocation mechanism which is a critical early step in the development of the disease, through detailed analysis of the breakpoints on chromosomes 15 and 17 [References 1,2 below].

The KCL group's work on the 10% of patients who do not show the typical rearrangement between chromosomes 15 and 17 has also had a considerable impact. This is because analysis of samples taken from these patients during diagnosis showed that the *PML-RARA* fusion gene is usually still the underlying abnormality [3,4], which means that such patients can still be successfully treated with ATRA and arsenic.

There are other less common fusion genes which can cause APL, an important point because which fusion gene is involved influences the way the disease behaves and which treatments may be effective. The KCL group has therefore also investigated rearrangements on chromosomes 11 and 17 in which *RARA* is fused to the *PLZF* gene [5]. In this subtype of APL, ATRA and arsenic will not be effective. Molecular diagnosis in patients with suspected APL is therefore critical to identify patients likely to benefit from particular molecularly-targeted drugs.

Research supporting the monitoring of APL: The key to tracking patients' response to treatment, and so providing early warning of recurrence after treatment, was found when the KCL group identified the fusion gene transcripts expressed in leukaemic cells in APL. Polymerase chain reaction (PCR) is a biochemical technique that multiplies a single or a few copies of a piece of

DNA by the million, allowing them to be easily detected. Development of successful PCR assays for *PML-RARA* and reciprocal *RARA-PML* transcripts led to their use as targets for detecting small numbers of leukaemic cells remaining in the patient after treatment—known as minimal residual disease (MRD) [6, 7]. Regular MRD monitoring for *PML-RARA* genes using PCR assays alerts doctors to the very first signs of disease recurring. They can then treat patients early, thus avoiding the significant risk of death due to the bleeding disorder associated with APL.

This internationally excellent work by KCL has been widely incorporated into clinical care. It is now recognised that MRD monitoring can provide accurate predictions of the likely outcomes for APL patients during treatment. In the 1990s, more sensitive PCR assays became available, allowing treatment responses to be tracked far more precisely. Exploiting this advance in technology, Prof. Grimwade has played a leading role in the design, optimisation and standardisation of PCR assays for APL and other myeloid neoplasms (including *PML-RARA, JAK2-V617F*) [8-10].

3. References to the research

1. Mistry AR, Felix CA, Whitmarsh RJ, Mason A, Reiter A, Cassinat B, Parry A, Walz C, Wiemels JL, Segal MR, Ades L, Blair IA, Osheroff N, Peniket AJ, Lafage-Pochitaloff M, Cross NC, Chomienne C, **Solomon E**, Fenaux P, **Grimwade D**. DNA topoisomerase II in therapy-related acute promyelocytic leukemia. *N Engl J Med.* 2005:352:1529-38.
2. Mays AN, Osheroff N, Xiao Y, Wiemels JL, Felix CA, Byl JAW, Saravanamuttu K, Peniket A, Corser R, Chang C, Hoyle C, Parker AN, Hasan SK, Lo-Coco F, **Solomon E**, **Grimwade D**. Evidence for direct involvement of epirubicin in the formation of chromosomal translocations in t(15;17) therapy-related acute promyelocytic leukemia. *Blood*. 2010:115:326-30.
3. **Grimwade D**, Gorman P, Duprez E, Howe K, Langabeer S, Oliver F, Walker H, Culligan D, Waters J, Pomfret M, Goldstone A, Burnett A, Freemont P, Sheer D, **Solomon E**. Characterization of cryptic rearrangements and variant translocations in acute promyelocytic leukemia. *Blood*. 1997;90:4876-85.
4. **Grimwade D**, Biondi A, Mozziconacci M-J, Hagemeijer A, Berger R, Neat M, Howe K, Dastugue N, Jansen J, Radford-Weiss I, Lo-Coco F, Lessard M, Hernandez J-M, Delabesse E, Head D, Liso V, Sainty D, Flandrin G, **Solomon E**, Birg F, Lafage-Pochitaloff M. Characterisation of acute promyelocytic leukemia cases lacking the classical t(15;17): results of the European Working Party. *Blood*. 2000;96:1297-308.
5. Guidez F, Parks S, Wong H, Jovanovic JV, Mays A, Gilkes AF, Mills KI, Guillemin MC, Hobbs RM, Pandolfi PP, de Thé H, **Solomon E**, **Grimwade D**. RARα-PLZF overcomes PLZF-mediated repression of CRABPI, contributing to retinoid resistance in t(11;17) acute promyelocytic leukemia. *Proc Natl Acad Sci USA.* 2007;104:18694-9.
6. Jovanovic JV, Rennie K, Culligan D, Peniket A, Lennard A, Harrison J, Vyas P, **Grimwade D**. Development of real-time quantitative polymerase chain reaction assays to track treatment response in retinoid resistant acute promyelocytic leukemia. *Front Oncol.* 2011;1:35.
7. Burnett AK, **Grimwade D**, **Solomon E**, Wheatley K, Goldstone AH. Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: result of the randomized MRC trial. *Blood*. 1999;93:4131-43.
8. Gabert J, Beillard E, van der Velden VHJ, Bi W, **Grimwade D**, Pallisgaard N, Barbany G, Cazzaniga G, Cayuela JM, Cavé H, Pane F, Aerts J L E, De Micheli D, Thirion X, Pradel V, González M, Viehmann S, Malec M, Saglio G, van Dongen JJM. Standardization and quality control studies of 'real-time' quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia – A Europe Against Cancer Program. *Leukemia*. 2003;17:2318–57.
9. **Grimwade D**, Jovanovic JV, Hills RK, Nugent EA, Patel Y, Flora R, Diverio D, Jones K, Aslett H, Batson E, Rennie K, Angell R, Clark RE, **Solomon E**, Lo-Coco F, Wheatley K, Burnett AK. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol.* 2009;27:3650-8.
10. **Grimwade D**, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, Rees J, Hann I, Stevens R, Burnett A, Goldstone A. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. *Blood*. 1998;92:2322-33.

Since 2001, over £4.6M of competitive grant funding was obtained by the KCL group for this work, including:

- National Institute for Health Research: £2M
- European Union (European LeukemiaNet): €191,800
- Leukaemia Research Fund (now Leukaemia & Lymphoma Research): £2.63M

4. Details of the impact

Marked improvements in outcomes for APL patients: Increased survival is the greatest impact resulting from this underpinning molecular research. In UK national trials, the percentage of APL patients surviving 5 years after treatment has risen from 56% in 1990 to over 90% in 2013.

Improved molecular diagnostics and the monitoring of 'minimal residual disease' (MRD) to guide targeted therapies have made significant contributions to the increased survival rates —in both of which the KCL research has played a major role (Section 2). In recognition of this, Prof. Grimwade was appointed to coordinate molecular screening and MRD monitoring in the UK National Cancer Research Institute (NCRI) AML trials. The improvement in survival is also due to the introduction of molecularly-targeted drugs, an area to which KCL research on the underlying molecular causes of APL has also contributed (Section 2).

Specific impacts of the strategy developed by KCL for monitoring MRD were seen in national trial MRC AML15. Compared with the previous trial in that series, in which MRD was not monitored, the KCL strategy halved the number of patients suffering a full-blown recurrence of APL. Importantly, monitoring MRD led to a significant increase in overall survival, especially in patients who had high-risk disease: it gave a 10% survival advantage after 5 years at a cost of only £1.35k per quality-adjusted life year gained (see [9] above).

Findings used in international and national treatment guidelines: Grimwade et al.'s findings have been used to personalise treatment for APL, based on risks faced by individual patients [11]. The original risk classification [10] developed by KCL researchers in national trials—based on the chromosome defects found in different subtypes of AML—has had considerable impact in shaping approaches to treatment in the UK and elsewhere (in addition, that paper has been cited over 2000 times). The classification system was further refined in 2010 after analysis of almost 6000 younger adult patients with AML; this is already guiding decisions about the value of conducting bone marrow transplants.

This KCL work has had a very significant impact, informing international APL treatment guidelines [12], which recommend molecular diagnostics as mandatory for successful patient management.

MRD monitoring is now also recommended in the US National Comprehensive Cancer Network guidelines [13], with molecular monitoring of disease response recognised as a standard of care.

Assays based on KCL research used widely in the NHS and across Europe: The molecular diagnostic and monitoring assays that were validated by the KCL group have now been implemented within the NHS, with Guy's Hospital continuing to serve as a hub for analysis [14] and also as the reference centre for the National Cancer Research Institute (NCRI) leukaemia trials.

Prof. Grimwade is Chair of the European Hematology Association Scientific Working Group on AML and leader of the Minimal Residual Disease component of the European LeukemiaNet [15] (EU 6th Framework, Network of Excellence), coordinating 28 expert laboratories, spread across 12 countries. This has extended across Europe the use of the optimised assays that can be used to track MRD in patients with blood cancers [15]. It has also fostered the development of a tailor-made software package to report patient results in a standardised manner [16]. This software has also been used to report MRD data in the UK NCRI AML trials.

Assays based on KCL research used in UK and European clinical trials: Apart from routine care, these assays are also being employed in the UK's national AML17 trial [17] and in the European ICC01 trial [18] which is run by I-BFM and which targets children who have APL. In these trials, MRD monitoring is being used as a safeguard to determine whether drug use in APL treatment can be cut down, in order to reduce toxicity while still maintaining high cure rates.

Media coverage and public dissemination of KCL work on MRD monitoring: The implications of the KCL research have been disseminated to the public [19-21] and covered in the lay press [22-23].

5. Sources to corroborate the contribution, impact or benefit

International disease guidelines based on KCL group's work

11. Tallman M, Douer D, Gore S, Powell BL, Ravandi F, Rowe J, Ranganathan A, Sanz MA. Treatment of patients with acute promyelocytic leukemia: a consensus statement on risk adapted approaches to therapy. *Clin Lymphoma Myeloma Leuk.* 2010;10 Suppl 3:S122-6.
12. Sanz MA, **Grimwade D**, Tallman MS, Lowenberg B, Fenaux P, Estey EH, Naoe T, Lengfelder E, Büchner T, Döhner H, Burnett AK, Lo Coco F. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2009;113:1875-91.
13. National Comprehensive Cancer Network (NCCN [USA]) AML practice guidelines: https://subscriptions.nccn.org/gl_login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (pages MS5-6, reference to Grimwade et al. page MS39).

Diagnostic test validated by KCL research group and used by NHS

14. PML-RARA testing from GSTS Pathology: http://gsts.com/test-search-results.html?search_department=Molecular+Oncology&search_keywords=

Grimwade's leadership of international scientific groups and development of software tool to report MRD data based on KCL work

15. European LeukemiaNet, Chair of Workpackage 12 on MRD: http://www.leukemia-net.org/content/home/eln_structure/index_eng.html#ZMS_HIGHLIGHT=raw&raw=grimwade
16. Østergaard M, Nyvold CG, Jovanovic JV, Andersen MT, Kairisto V, Morgan YG, Tobal K, Pallisgaard N, Ozbek U, Pfeifer H, Schnittger S, Grubach L, Larsen JK, **Grimwade D**, Hokland P. Development of standardized approaches to reporting of minimal residual disease data using a reporting software package designed within the European LeukemiaNet. *Leukemia*. 2011; 25:1168-73.

Clinical trials using minimal residual disease (MRD) approach

17. UK National Cancer Research Institute AML17 trial: http://aml17.cardiff.ac.uk/aml17/
18. International BFM Study Group ICC APL01 study: http://www.bfm-international.org/organization/aml.php

Public dissemination through the Leukaemia & Lymphoma Research (LLR)

19. Grimwade presentation at Leukaemia & Lymphoma Research (LLR) 'Impact Day' 2013 (p.6): http://leukaemialymphomaresearch.org.uk/sites/default/files/impact-day-programme-2013.pdf
20. King's College London as a LLR 'Centre of Excellence': http://leukaemialymphomaresearch.org.uk/research/our-centres-excellence/kings-college-london
21. LLR Patient leaflet: http://leukaemialymphomaresearch.org.uk/sites/default/files/apl_nov_2011_1.pdf

M**edia coverage**

22. MRD monitoring to deliver personalised medicine in AML: http://www.healio.com/hematology-oncology/hematologic-malignancies/news/print/hematology-oncology/%7B19ff31b3-08b5-4456-8bbc-bfad6f196a3f%7D/research-highlights-move-toward-personalized-treatment-in-aml

23. Development of standardised assays to track residual disease in myeloproliferative neoplasms: http://www.curetoday.com/index.cfm/fuseaction/news.showNewsArticle/id/5/news_id/3811