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OBITUARY

Professor David Grimwade (1962–2016)

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David Grimwade had a remarkable impact on the care of patients with acute myeloid leukaemia (AML) during his career. Possessing a skillset that combined clinical knowledge and expertise with a profound insight into the applicability of basic science to clinical medicine, he was in many ways the embodiment of the translational haematologist. Coupled with his exceptional generosity and tireless commitment to improving individual patient outcome, his career provided a compelling demonstration of the ever-expanding opportunities to improve patient outcomes through the application of science.

Educated at St Edward's School, Reading, and then at Oxford University, David went on to read Medicine at St Mary's Hospital Medical Hospital in London and for the rest of his medical career worked in hospitals in and around London. He first became interested in Haematology through attending morphology lectures as an undergraduate at St Marys and subsequently, as a house physician, he was fascinated by both the diversity and clinical complexity of haematological diseases and the central role of the laboratory in securing diagnoses and monitoring response to therapy. After general medical training in Oxford and a spell at the Royal Marsden Hospital as a Junior Lecturer he obtained a Registrar training post at University College Hospital in London. He once joked that the scrutiny endured by the presenting registrars at the large Monday morning ward rounds at UCH stood him in good stead for answering questions when presenting at international conferences. David's first full-time involvement in research was on an MRC Clinical Training Fellowship at the ICRF with his supervisor and later mentor Ellen Solomon at the Cancer Genetics laboratory at Guy's Hospital, King's College London, an institution where he would go on to spend most of his working life. It was evident from early on during his research training that David would be able to combine that elusive aim for most clinician scientists, achieving advances in the basic science of leukaemia and in the process making a major contribution to the treatment of AML. His work led to influential publications on the importance of diagnostic cytogenetics on outcome in AML in addition to focussing on his research interests of the molecular pathogenesis of acute promyelocytic leukaemia (APL) and characterizing mechanisms underlying leukaemia-associated chromosomal translocations. He was among the first to characterize the PML-RAR fusion gene of APL and to track the fusion gene during therapy, working with international collaborators such as Francesco Lo Coco.

In 1999 David obtained the prestigious Leukaemia Research Fund Bennett Senior Research Fellowship at the GKT School of Medicine, Kings College London, where he went on to be appointed Senior Lecturer in 2001 and then Professor of Molecular Haematology in 2007. His work on the basic biology of APL led to another critical study published in the *New England Journal of Medicine* in 2005 on the mechanisms of therapy-related APL. This was only one of many contributions that encompassed both the biology and prognostic impact of genetic factors in AML. David's approach to his research and that of others included a meticulous attention to detail and perfectionist streak. That included what became a legendary ability to find errors, including minor typos when reading manuscript drafts and PhD theses. Not surprisingly, he was a valued and much-used reviewer by journal editors.

In 1995 he joined the Medical Research Council (now NCRI) AML Working Group which allowed him further to develop his translational research interests in AML particularly, the use of molecular techniques for minimal residual disease detection, a subject on which he became a leading international authority. He coordinated MRD monitoring in the UK National Cancer Research Institute AML trials and collaborated with research groups via the European LeukemiaNet in the development of real-time quantitative PCR. Initially this approach was in APL, but over the last few years had extended to an array of other molecular types of AML. In 1999 he reported on the experience of the early identification of disease recurrence in APL and the clinical benefits resulting from pre-emptive therapy at the time of molecular relapse. The approach was further developed in the MRC AML15 and 17 trials, where he was responsible for MRD monitoring of all APL patients. This experience led to his passionate belief in the value of MRD monitoring to improve clinical outcome. He remained closely associated with the treatment and monitoring of APL and was part of an expert panel on behalf of the European LeukemiaNet, which published important guidelines on treatment and management of the disease. With Alan Burnett he developed the AML17 trial APL concept of using chemo-free treatment in newly diagnosed patients. Although AML17 failed to show an overall survival advantage for the chemo-free option with arsenic trioxide compared to chemotherapy, this was in part due to the effectiveness of salvage treatment for the chemotherapy arm given at the time of early molecular relapse as predicted by the Grimwade lab. All the APL patients in the trial underwent MRD monitoring, with the results emailed back along with interpretation to the investigators at the over 100 individual collaborating

sites. Without this effort it is likely that many more patients in the chemotherapy arm would have had a haematological relapse with predictable consequences. These results were often sent on a Friday afternoon or over the weekend, and it was common to receive a torrent of e-mails from David concerning MRD results regardless of whether he was in the UK or travelling. These were only interrupted by his Saturday afternoon trips to support Reading Town Football Club, usually accompanied by one of his daughters, as his team made their annual unsuccessful attempt to be promoted to the premier division. Through this unobtrusive commitment to patient care David not only quietly but also authoritatively influenced the management of thousands of patients with APL, and he also demonstrated how important, and potentially powerful in terms of generating primary research data, regular and thoughtful interaction with individual clinicians at large and small hospitals could be.

Over the last few years David had extended his MRD interest beyond APL and was using molecular techniques to track leukaemia fusion gene transcripts in other types of AML, and in 2016 published a study showing that the assessment of minimal residual disease in patients with AML and known NPM1 mutations provided prognostic information that was independent of other risk factors. This seminal work published in the *New England Journal of Medicine* in 2016 demonstrated that the use of MRD could help risk stratify patients with NPM1-positive disease, which can help decision-making concerning transplantation or not in standard-risk AML.

One of the defining characteristics of David's professional career was the enjoyment he derived from interacting and collaborating with his colleagues internationally. He also developed the art of efficient air travel and finding the best restaurants to enjoy with his haematology friends when abroad. Moreover, with his European colleagues he could indulge in discussions both on football and on wine. It was therefore a natural fit that he should be one of the founder members of the European community-funded initiative of the European LeukemiaNet, leading the MRD Work Package, a network of labs spread across 12 countries. Steered by him the working group was inclusive and jointly achieved the careful development, standardisation and quality control studies of several quantitative PCR assays that are now a critical part of leukaemia management. David recognised early the importance of harmonisation in leukaemia monitoring as long as done well without compromising the results. He was always kind, open and straightforward when working with others (including sometimes sharing his frustrations with the obstacles to generating good-quality data), made sure that his colleagues were fully recognised for what they contributed, as well as very generous in sharing opportunities that were offered to him. He was articulate and entertaining in debates about MRD monitoring and stood his ground for what he believed advanced the management of leukaemia. His input into mentoring junior colleagues as exemplified by his role at the ASH/EHA Translational Research Training Institute was as unstinting as his clinical help for the more complex molecular diagnostics and interpretation of molecular assays. It is appropriate that in the last few months of his life international recognition has been forthcoming, from the European Haematology Association with a lifetime achievement award, from ASH with an exemplary service award and from the European LeukemiaNet with the ELN Merit-Award

Typically for David he continued to contribute to the ELN and international community at meetings until the very last weeks of his illness, with resilience, humour, kindness, pragmatism and dedication. As Gert Ossenkoppele said following his death 'The death of David is an enormous loss for the hematology community because of his great contribution to hematology field but even more important because we lose a unique and highly respected friend.' His demonstration of how combining clinical excellence with scientific insight can transform patient outcomes in the 21st century will continue to inspire us all.

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