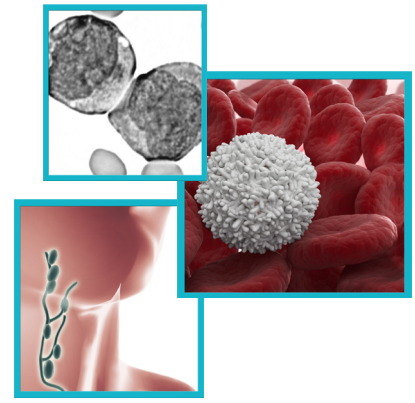
‘Familial’ chronic lymphocytic leukemia



Chris Pepper* speaks to Roshaine Gunawardana, Managing Commissioning Editor: Dr Chris Pepper obtained his PhD in Medicinal Chemistry from the Welsh School of Pharmacy (Cardiff, Wales, UK) in 1993. He completed his postdoctoral training in the Department of Pathology at Cardiff University, School of Medicine (Cardiff, Wales, UK) before moving to Llandough Hospital (South Glamorgan, Wales, UK) as a Clinical Scientist in Hematology. He is currently a Reader in Hematology in the Institute of Cancer & Genetics in Cardiff where he runs a successful research team and provides the high-speed cell sorting facility for the University. For the past 18 years, his research career has been focused on chronic lymphocytic leukemia. During this time, he has published over 80 peer-reviewed papers and has been an invited speaker at numerous national and international meetings. His research team is currently addressing basic, translational and clinical questions in chronic lymphocytic leukemia. These include investigations into the mechanisms that underpin the development of disease progression and drug resistance, elucidation of novel biomarkers of prognosis in order to provide superior risk stratification for individual patients, and the development of novel targeted therapeutic agents.

Q What particularly led to your specific interest in the field of hematology, and in particular chronic lymphocytic leukemia?

My father was diagnosed with chronic lymphocytic leukemia (CLL) whilst I was studying for my PhD. Until that point I was contemplating a career as a breast cancer researcher, but that event led me to change my mind and turn my attention to leukemia.

Q Can you identify any mentors or other individuals who have had a specific impact on the directions you have taken scientifically?

I have been incredibly lucky throughout my career to work with clinicians/scientists who have encouraged me to pursue my own ideas. As a junior postdoc, I worked with Paul Bentley (LLandough Hospital, South Glamorgan, Wales, UK) and for the last 12 years I have had the great fortune to work with Chris Fegan (Cardiff University, Wales, UK). Beyond my immediate working environment, my career has been significantly influenced by the work of John Reed (Sanford-Burnham Medical Research Insititute, CA, USA), Freda Stevenson (University of Southampton, UK) and Nick Chiorazzi (The Feinstein Institute for Medical Research, NY, USA) – all of whom have made massive contributions to the field of CLL research.

Q To date, what do you think are your greatest achievements within the field of hematologic oncology?

I don’t actually feel that I could identify a ‘greatest achievement’ – I consider myself to be a solid but unremarkable scientist if truth be told. I’d like to believe that I have made a few modest contributions to the

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field over the last 18 years, but I would prefer to point to the work of the people I mentioned previously for those 'eureka' moments. If I was forced to highlight one contribution that I am most proud of, I would probably say the work we have done on BCL2 family proteins, as I still believe that targeted inhibition of these molecules may hold the key to the more effective therapies for this disease.

Q Your research group is involved with looking at the role of the BCL2 family of proteins in CLL, in addition to B-cell receptor and coreceptor signaling. Could you briefly describe the aims and any outcomes of ongoing experiments?

Our research can be divided up into three broad categories: biomarker discovery and validation; basic tumor cell biology; and novel therapeutic development. I would like to believe that the three areas are linked such that the discoveries we make about tumor cell biology help us to identify rational drug targets that can in turn be used as biomarkers of response to treatment. A good example of this is our interest in the transcription factor NF-κB. We initially established that this family of proteins is constitutively overexpressed in CLL when compared with normal lymphocytes, and B-cell receptor signaling could further enhance the expression. This led us to work on novel NF-κB inhibitors as potential therapeutics, one of which is now in early phase trials in CLL. Subsequently, we showed that NF-κB plays an important role in the development of drug resistance, and the expression of a subunit called RelA is an independent prognostic marker for survival in this disease. Our current work is focused on dissecting the precise role that individual NF-κB subunits play in the regulation of important cellular processes – for example, proliferation, migration and survival. An important facet of this work is the development of more relevant *in vitro* model systems that more accurately reflect the *in vivo* microenvironments that CLL cells live in.

I firmly believe that CLL represents an unrivalled primary human tumor model for investigating apoptotic signaling pathways and the molecular mechanisms that promote drug resistance. The ability to derive serial samples from individual patients also facilitates the longitudinal analysis of tumor cell evolution at the genetic, transcription and proteomic levels. Most recently, we have begun to address questions relating to cytogenetic instability and clonal evolution in collaboration with Duncan Baird (Cardiff University). Using Baird's expertise in telomere biology, we have shown that CLL cells have some of the shortest telomeres ever described in a human malignancy. Importantly, these short telomeres can become dysfunctional resulting in telomeric fusions, and these events were accompanied by large-scale genomic rearrangements. These data led us to conclude that telomere erosion, as a consequence of CLL cell division, results in significant telomere dysfunction that may drive genomic instability and disease progression. Our ongoing research in this area is focused on the role of telomere dynamics in disease progression, clonal evolution and in modulating response to chemotherapy.

Q Your research is entirely patient-focused. How important do you believe it is for research in this field and related areas of oncology to be increasingly patient-focused, and what are the benefits of this approach?

If we are not doing the research we do for the benefit of patients then I question why we are doing it at all! Of course, cell lines are great tools for dissecting out the specific role of individual molecules or pathways, but they are not at all representative of real patient disease. Consequently, I have always been committed to working on primary patient material. Clearly there are significant challenges associated with this approach, but I firmly believe that the advances that have been made in CLL over the last few decades have come about because of consistent research on patient-derived cells and a constant focus on clinically relevant questions. Besides the obvious biological benefits of working with clinical material, there are human benefits too. Many of the patients who donate their blood for our research are incredibly interested and enthusiastic about what we are doing with their cells, and that is a real inspiration and encouragement to everyone in the team.

Q What are the next steps for your research?

Besides all of the active lines of investigation that I have already mentioned, we are now trying to apply some of the knowledge that we have gained in CLL into other B-cell malignancies, including multiple myeloma and mantle cell lymphoma. Over the next few years, I suspect that we will also be involved in more early-phase clinical trials of some of the new targeted therapies that are now starting to emerge, so very exciting times ahead I'm sure!

Q How would you like to see this area of research developing in the future?

For the first time in my research life I can envisage a time when we will be able to offer curative therapies to patients with CLL. The emergence of rationally designed, targeted inhibitors of signaling pathways, BCL2 family members, NF-κB subunits and cyclin-dependent kinases, as well as the next generation of fully humanized monoclonal antibodies, really will change the landscape, I'm certain. Of course there is still much work to do, particularly in identifying the optimal combinations and scheduling of these new agents, as well as establishing robust response biomarkers, but I am genuinely optimistic that a revolution in personalized CLL therapies and prognostication is just around the corner.

Financial & competing interests disclosure

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