Scientific & Clinical

2009 WALDENSTRÖM'S AWARD

Dr. Brian G.M. Durie is Honored for a Lifetime of Achievement in Myeloma

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Dr. Durie, congratulations on being the 2009 recipient of the prestigious Waldenström's Award for lifetime achievement. The award, named for Prof. Jan Waldenström, a pioneer in treating blood cancers, was bestowed at the opening of the XIIth International Myeloma Workshop in Washington, DC. As recipient, you presented the traditional Waldenström's Award Lecture, and we would like to ask you about what you discussed in your talk.

I was truly honored to receive the Waldenström Award, and very thankful to all those who made it possible. In my Waldenström Lecture, I touched upon some of the reasons that I might have been standing at that podium, and summarized the key developments in the field of myeloma from when I first started working on this disease through the present day. In addition, I assessed how I see things moving forward. I have been working on myeloma for 40 years and, in my lecture, I tried to convey some of the lessons I've learned along the way.

What have been some of those lessons?

When I studied at the University of Edinburgh, anatomy was a major part of the program. I am a clinician at heart, and understanding anatomy has served me well over the years when trying to identify what might be wrong with an individual patient.

When I worked at the Mayo Clinic in Minnesota, it was very clear that for all the research being performed at that institution, the patient always remained the number one priority. I have never lost sight of this in the years that have followed. That ethos is key to the Mayo Clinic, and it is reflected in Bob Kyle and his colleagues, as well as in

all the doctors who have passed through the Mayo Clinic over the years and those who work there today.

At the University of Arizona, I was recruited by Sydney Salmon to work on the myeloma staging system. At that time, Syd was working on a method of measuring myeloma cells in the body. Myeloma was unique in that it was possible to calculate the number of cancer cells based upon the amount of monoclonal protein produced, and to correlate the total number of myeloma cells with the physical features that a patient manifested. In 1977, we established the first myeloma clinic there and, over the following years, I pursued a variety of projects at my myeloma laboratory.

After many years at the University of Arizona, I moved back to the UK to become head of the Haematology Department at the University of London. Three or four years later, I came back to the US and settled in Los Angeles. There, the International Myeloma Foundation, which was started while I was still in London, became a major commitment for me. The IMF mission of being dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure has remained a focus for me for the last 20 years.

Much of your work in the field of myeloma over the decades is still important today. Your work on the Myeloma Staging System dates back more than 30 years!

The Myeloma Staging System took two years to develop and was published in *CANCER* in 1975. That was my first major published paper. I applied statistics to the analysis of myeloma outcomes. The lesson of that work was that applying new techniques to old problems can lead to progress. The correlations that we made all those years ago, applied to a relatively small data set, are still true today.

Another example of a concept that has remained relevant is that myeloma can enter a plateau phase. Would you please tell us about that?

In 1980, *THE LANCET* published my paper on the plateau phase in myeloma. Intrinsically, myeloma is not always actively growing. The plateau phase is an indolent phase during which no new myeloma growth is occurring. It is possible to stop treatment during the plateau phase, with the disease remaining stable for two or three years or sometimes longer. That's an important concept in terms of maintenance

therapy and, yes, that crucial point has persisted to the present time. For patients in the plateau phase, the "standard of care" is no maintenance because maintenance therapy does not offer clear added advantage.

In the years that followed, you worked on understanding amyloid, Sß2M, and osteoclast activating factors and bone disease.

In the 1970s, Gregory Mundy and I worked on osteoclast activating factors. That work was the first recognition of myeloma-derived factors triggering bone disease. At that time, we did not know exactly what those factors were, but we were able to demonstrate that when fluid from myeloma is added to bone it causes bone destruction, and that the extent of the bone disease is quantitative. Our paper was published in the *British Journal of Haematology* in1981 and was the starting point for subsequent studies looking at myeloma bone disease. Greg Mundy went on to identify several of the bone resorptive factors.

In 1982, the *New England Journal of Medicine* published my paper on amyloid production in human myeloma stem-cell culture. By observing myeloma stem-cell cultures in the lab, we were able to show, by electron microscopy, amyloid synthesis (production) as a result of myeloma cells' macrophages.

My work on serum beta2-microglobulin (Sß2M) plus albumin, which was the result of collaboration with Regis Bataille, showed that Sß2M reflects myeloma biology. Our paper was published in *Blood* in 1986 and, 20 years later, served as the basis for the International Staging System (ISS) of myeloma.

In 1988, I published a paper in the *British Journal of Haematology* on overcoming multi-drug resistance (MDR) in myeloma with verapamil. This was not the result of a protocol I was working on, but rather the outcome of my experience with a myeloma patient who had to be treated with verapamil for her high blood pressure while she was receiving VAD chemotherapy for her myeloma. I subsequently worked with cyclosporine, a drug that was even better at overcoming MDR than verapamil, and I published several papers on this together with Pieter Sonneveld.

In 1989, I started collaborating with Howard Urnovitz on the SV40 polyomavirus (found in the rhesus monkey kidney cells used to make the polio vaccine) and circulating RNA

in microvesicles in myeloma. Our work led to a more detailed evaluation of RNA sequences present in the blood of people with myeloma. The project is moving forward with new technology that has made it possible to detect all of the sequences present in blood. Now, having looked at all the sequences using the new technique, we have been able to confirm that the sequence we had found in the late 1990s using what amounts to calculated guesswork is in fact the relevant sequence for myeloma. The on/off "switch" for myeloma varies from patient to patient, and this work is bringing us much closer to identifying the molecular signature of myeloma on an individual patient basis.

In the 1980s and 1990s, I studied all sorts of things with the soft agar culture -- drug sensitivity, labeling index, etc. We had the first cytogenetics lab devoted exclusively to myeloma and related diseases, and we studied cytogenetics on each of our myeloma patients. Many papers were published as a result of our research, and many sank like a stone thrown into a dark well.

How is that possible?

It is not unusual for valid ideas to languish for decades. By definition, new concepts may not directly fit in with what others in the myeloma field are working on so, unless you continue to work on the concepts yourself, the ideas may not be picked up by others for many years.

In 1984, the *British Journal of Haematology* published my work on myeloma heterogeneity, which examined whether myeloma is or is not a monoclonal disease. In that paper, I pointed out that while myeloma cells tend to continue to produce the same monoclonal protein, the disease is heterogeneous and evolves over time. This point is confirmed by patients who become non-secretory and those who develop extra-medullary myeloma in the course of their disease. We see heterogeneity in disease that becomes resistant to treatment. When a patient becomes resistant to a previously effective treatment, we see that the presence of the monoclonal protein is deceptive, because it makes you think that the disease is the same, while in fact the genetics have changed. I was able to show this at a molecular level. In 1984, I demonstrated that myeloma is polyclonal from the genetic perspective, manifesting sequential clonal evolution. The cells don't even look the same over time. Today, when myeloma researchers are looking at chromosomal deletions and translocations, it is clear that we are dealing with sequential clonal changes and a disease that is actually heterogeneous.

It is crucial that we acknowledge that there is a tendency for this to happen, because it is myeloma's strong heterogeneity that makes it a tricky disease and accounts for its bad prognostic features.

Along the same lines, we can look at my collaboration with Benjamin Van Camp in the 1980s, when he worked in my lab in Arizona. We looked at the myeloma phenotype and reported that myeloma is CD56 positive. This was substantiated by two separate labs, including one that was a repository for the Southwest Oncology Group (SWOG), one of the largest of the National Cancer Institute-supported cancer clinical trials cooperative groups in the US. When we submitted our paper for publication in *Blood*, it was initially rejected because it was considered "not possible" for myeloma to share an antigen present on nerve cells. So we supplied further data from the world's two top labs confirming our findings with methods employing immunogold markers, and the manuscript was finally published in 1990, with the image from the rejected manuscript used for the cover photo! It took us years to convince others that the publication was valid and that the assertion in our original paper was in fact correct.

There are many other examples, as these experiences are not unique. New ideas are often rejected initially if they show an unexpected result. There have been several instances where I would be contacted by someone who had done the same research I did many years ago but who was unaware of my work until after they had completed their own research and did a literature search and found my published papers.

Has this dynamic persisted to the present day?

At present, the dynamic in the field of myeloma is dramatically different, as we have worked hard to establish very active collaboration. The International Myeloma Working Group (IMWG) is the result of those efforts. Now, a promising new idea in myeloma will be immediately investigated and validated by others. In fact, over the last five or six years, important projects have been initiated in collaboration with the IMWG, which have produced a whole series of manuscripts.

You have also worked on PET scanning for many years. In fact, you received the 1st prize award for Best Nuclear Medicine Paper of 2002.

I started work with FDG (fluoro-2-deoxy-D-glucose) PET (positron emission

tomography) scanning in 1997 and published the paper you are referring to in the *Journal of Nuclear Medicine* in 2002. PET scans can improve disease staging and treatment planning, and can significantly change the course of treatment for many myeloma patients. With PET scans doctors can visualize the whole body to see the full extent of disease on initial diagnosis, follow the response to treatment more accurately, and better determine when further treatment is needed and when it is not.

Recently, PET scanning in myeloma was finally approved by Medicare for insurance coverage. It took a decade to get this accomplished. As you might imagine, Medicare waged a battle of attrition against the approval: they called for meetings upon meetings where I had to plead the case for the use of PET scanning in myeloma. In the beginning, I would see representatives of many other cancer groups at the Medicare meetings who were trying to get PET scanning approved for various diseases. At the last meeting, I was the only one representing myeloma, and the only other person in attendance representing a disease group was an advocate for ovarian cancer. She and I were the only ones there to present our cases and, in the end, Medicare approved PET scanning only in myeloma and ovarian cancer. Clearly, perseverance paid off! The cancer groups that had given up were denied approval, although the technology might have been useful for them as well.

What do you see as you look toward the future?

Luc Montagnier, who first identified the AIDS virus, is working with Howard Urnovitz and me on sequencing DNA and RNA in the blood; Luc has called these circulating nucleotides "Voyager DNA" and "Voyager RNA." It is possible to identify molecular patterns of disease that will be an important way to both diagnose and monitor myeloma on an individual patient basis. I am very interested in this project as I believe it will lead to new approaches to cancer therapy. This would be a very important way forward.

Innovation is always challenging. In addition to the usual difficulties, the present economic climate has placed additional challenges in our path. But we must remain focused on our key goal -- improving outcomes for our patients -- so we must consider not only the cost of myeloma therapies but the cost effectiveness of therapies.

The stimulus for me as a clinician continues to be working with patients, thousands of

patients over the years. They continue to be my inspiration. MT