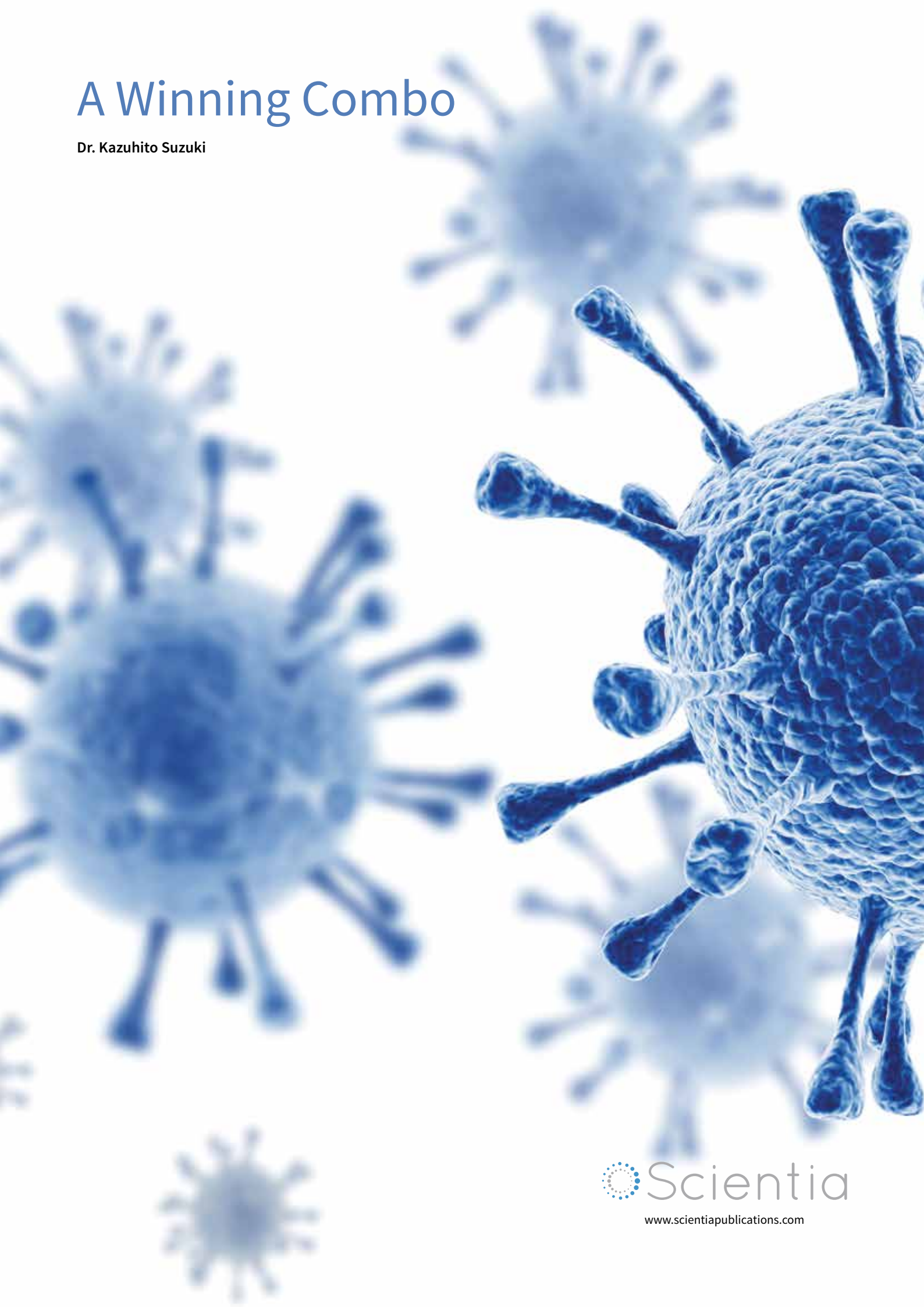
A Winning Combo

Dr. Kazuhito Suzuki



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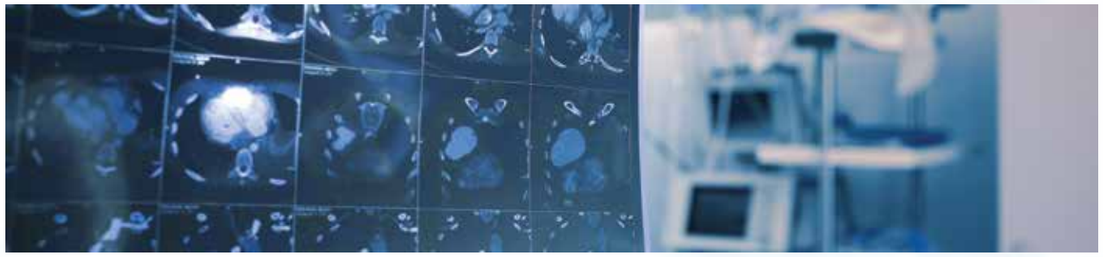
With a long term goal of abolishing multiple myeloma, Dr. Kazuhito Suzuki of the Jikei University School of Medicine, Japan, spends his time trying to identify the best treatments. Here, we ask him about the challenges in his work.



Could you discuss your background? What brought you into the field of oncology, and multiple myeloma research in particular?

I was greatly interested in multiple myeloma because I was entering the field just as we had significant progress in treatments for multiple myeloma. Bortezomib became available to patients with relapsed and refractory multiple myeloma in Japan just as I became a clinical resident, which really changed the treatment strategies available.

What was your most significant research finding so far?

My research findings from this trial indicate that the CLD regimen was very effective and tolerable in relapsed multiple myeloma patients. Moreover, if biochemical relapse occurred after entering the lenalidomide maintenance therapy, the CLD regimen became active again.

My findings from previous research demonstrated that thymidine kinase activity was related to overall survival in patients with newly diagnosed diffuse large B cell lymphoma or mature T cell lymphomas. I would like to extend this work by analysing the correlation between thymidine kinase activity and survival in patients with newly diagnosed multiple myeloma.

Have you experienced any obstacles doing your research and how did you overcome them?

Recruiting patients into this study was difficult because the inclusion criteria were very strict. Recently, we extended our candidate pool by decreasing the necessary haemoglobin concentration from 8.0 g/dL to 7.0 g/dL in our inclusion criteria. In general, I consider inclusion criteria to be one of the most important issues surrounding success in a clinical trial.

Your work focuses on therapy combinations, and their synergistic effects. Why did you choose to examine CLD + lenalidomide maintenance therapy? Do you intend to examine other therapeutic combinations in future?

In my opinion, bortezomib and lenalidomide are standard antimyeloma agents and thus should be optimally administered just before myeloma cells can develop resistance to anti-cancer compounds. Why did we focus on the combinations that we studied? Firstly, a goal of first-line and second-line chemotherapy is, naturally, to achieve as optimal a response as possible. A lot of studies had demonstrated that better response was achieved with this combination, including longer progression-free-survival and overall survival rates. Secondly, triplet chemotherapy regimens tend to show a superior response in patients when compared with doublet regimens.

Bortezomib had only been approved as an initial, first-line, chemotherapy in Japan. So, we selected bortezomib-containing regimens as our initial chemotherapy, and lenalidomide-containing regimens as the second line of treatment. Several studies had previously demonstrated that combinations of cyclophosphamide and lenalidomide were active and well tolerated.

One combination, comprising the Bortezomib, lenalidomide and dexamethasone (BLD) regimen, is considered a good option for salvage chemotherapy. However, for several reasons, I chose not to select the BLD regimen for salvage chemotherapy. First, a Phase 1/2 trial of BLD demonstrated that the maximum tolerated dose for lenalidomide was 15mg, whereas I consider that optimal salvage therapy dose of lenalidomide is 25mg daily for 21 days, as seen in the MM009/ 010 trial. Second, the BLD regimen is extremely expensive. Third, long-term lenalidomide maintenance therapy is controversial and in need of further research. Fourth, we omit dexamethasone wherever we can because long-term administration of dexamethasone can lead to increased infection rates. We wanted to demonstrate that dexamethasone is not necessary for maintenance in patients showing a good response to the CLD regimen. Because of this, I selected CLD regimens from the wide range of lenalidomide-containing options to identify whether it provided better results for patients.

How would you like to extend your research once this clinical trial is finished?

If I had a lot of research funding, I would like to perform a clinical trial in which anti-myeloma agents are selected in accordance with clonal evolution by next generation sequencing methods – personalised medicine for myeloma. For example, proteasome inhibitors are selected for XBP-1 over-expressing myeloma cells, or IMiDs is selected to treat cereblon-overexpressing myeloma cells. However, for the present, we would like to collaborate with other specialist teams in order to relieve patients' symptoms. Our next project involves performing plasma exchange combined with bortezomib containing chemotherapy to treat cast nephropathy in myeloma patients.

What would be your 'dream' research project?

My dream is to cure multiple myeloma. However, current treatments utilising proteasome inhibitors and IMiDs alone are not enough to cure all patients. Immunological approaches, such as CART therapy, are necessary stages even after patients demonstrate a good response to chemotherapy such as proteasome inhibitor and IMiDs.

Multiple Medicines For Multiple Myeloma

One of the major private medical schools in Japan, the Jikei University School of Medicine is involved in a number of facets of medical research. Work in the Clinical Oncology group has led to significant improvements in cancer treatment, such as that of multiple myeloma.

Multiple myeloma is the second-most common blood-derived cancer in the USA, caused by uncontrolled growth of the antibody-producing white blood cells (known as plasma cells) within the bone marrow. This results in a variety of symptoms: normal blood cell production is affected, leading to anaemia; persistent bone pain occurs as they are broken down by activated cells; while the large numbers of antibodies secreted by the overgrown plasma cells accumulate in the kidneys, damaging them and eventually leading to kidney failure. The disease remains incurable to this day, over half the patients who are diagnosed with multiple myeloma will be dead within five years.

Treatment of multiple myeloma involves therapies which can reduce the number of growing plasma cells, thus slowing the progression of symptoms. High-dose chemotherapy using compounds such as lenalidomide and bortezomib is used to prevent cell replication, sometimes assisted by targeted radiation therapy to wipe out the most persistent infestations. Patients can also be injected with stem cells (their own, or those from a healthy donor) which will then recolonise the now-empty bone marrow – going on to produce healthy cells.

However, while this process can lead to symptom relief and better quality of life, it is in many ways just a mirage, a temporary stay of execution. Plasma cell growth can be halted for a time, via drugs, radiation, or stem cell therapy. However, much like the monster from a bad horror film, the cancer will almost always come back. Even worse, the selective pressure exerted by the anti-cancer drugs will ensure that, much as bacteria develop antibiotic resistance, the surviving tumour cells will be resistant to the drugs which could previously kill it.

SILVER BULLETS

One approach to minimise this zombie-like resurrection of the cancer is known as maintenance therapy. First, the initial chemotherapy treatment knocks the number of plasma cells down to a reasonable level, some patients then have transplants of healthy stem cells to help them recover. Next, the patients begin to take a continuous, but lower drug dosage – the aim of this being to hold back any attempted revival by the remaining tumour cells. On the whole this approach works well, significantly increasing the time patients have in remission.

Unfortunately, there are some major downsides, particularly in that anti-cancer therapies are, by their very nature, toxic. As such patients on maintenance therapy often have numerous side effects which lower patient quality-of-life and can sometimes require cessation of the therapy. The question then becomes: how can we develop maintenance therapies such that they are effective, but with minimal long-term side effects?

Multiple myeloma remains incurable to this day, but research into optimal treatments is helping to extend patient survival time.

HUNTING MONSTERS

To answer this question we need to turn to clinical trials, in which researchers and physicians work together to identify the best therapies for patients in need of help. Two such trials are currently being supervised by Dr. Kazuhito Suzuki of the Jikei University School of Medicine, Japan. In particular, his group is studying the knockout effect of a triple-treatment known as CLD, followed by the lighter maintainance treatment of lenalidomide alone in relapsed or refractory myeloma patients

What have they discovered from this work? First, the CLD triple-treatment is very effective at knocking down the number of plasma cells, even in cases where patients have relapsed after prior treatment. Second, the lenalidomide maintenance treatment appears to be both effective (with a significant increase in patient survival after 4 years) and very well tolerated. As would be expected, some patients needed slight reductions in their long-term dosage, but on the whole the lenalidomide therapy caused minimal side-effects.

This is valuable information for scientists and physicians, as they need to balance both efficacy, side-effects, and cost. A common alternative to CLD, known as bortezomib, was at one stage rejected by the British National Health Service for its excessive cost (indeed, Dr. Suzuki chose to test CLD in part due to the expense of bortezomib). Having shown that the triple-treatment and maintenance program was both effective and well tolerated, this study allows doctors to confidently choose the less expensive treatment option, free of worries that it is somehow inferior.

Dr. Suzuki's dream is to find a cure for multiple myeloma. While this moment lies far in the future, getting to that point requires us to constantly improve our knowledge of treating the disease. Studies such as this are thus invaluable steps in our inexorable journey towards an ultimate remedy.

Researcher Profile

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Dr. Suzuki graduated from the Jikei University School of Medicine in 2006, after which he began his successful research career within the Clinical Oncology & Haematology Department. For 2 years he studied treatment strategies and research mind in the Cancer Institute Hospital of the Japanese Foundation of Cancer Research. His research focuses on drugs targeting multiple myeloma, in particular the ways in which these can synergise for greater efficacy.

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