POGOVOR Z NOBELOVIM NAGRAJENCEM SIROM GREGORYJEM PAULOM WINTERJEM

FOCUS ON WHAT TRULY MATTERS: INTERVIEW WITH SIR GREGORY PAUL WINTER

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Ponosni smo, da lahko v Farmacevtskem vestniku objavimo prepis ekskluzivnega pogovora z Nobelovim nagrajencem sirom Gregoryjem Paulom Winterjem, eno najvplivnejših oseb v biotehnologiji in farmacevtski znanosti. Z njim so se pogovarjali Anja Pišlar, Mojca Lunder in Tomaž Bratkovič, profesorji in raziskovalci na področju biotehnologije z Univerze v Ljubljani, Fakultete za farmacijo. Pogovor je potekal v angleškem jeziku in je objavljen v celoti, v slovenščini pa smo pripravili povzetek intervjuja.

Sir Gregory Winter, Nobelov nagrajenec in pionir na področju humaniziranih in humanih terapevtskih protiteles, je v intervjuju razkril pomembne vidike svoje kariere in dela. Njegovo delo je privedlo do razvoja terapij z monoklonskimi protitelesi za bolezni, kot so rak in avtoimunske motnje, ter navdihnilo raziskovalce in strokovnjake po vsem svetu. V svojem pogovoru je poudaril, kako ga je prejem Nobelove nagrade naučil previdnosti pri komuniciranju, saj ljudje njegove besede jemljejo zelo resno. »Za znanstvenika je to najvišje priznanje s strani kolegov znanstvenikov,« je priznal sir Gregory Winter. Prejema tudi veliko vabil za predavanja in poskuša navdihniti mlade znanstvenike, kadar je le mogoče. S tem nekaj vrne znanosti, ki mu je veliko dala. Razkril je tudi, kako so izkušnje v Cambridgeu in mentorji, kot sta bila Frederick Sanger (dvakratni prejemnik Nobelove nagrade za kemijo; 1958 in 1980) in César Milstein (prejemnik Nobelove nagrade za fiziologijo ali medicino; 1984), oblikovali njegovo raziskovalno pot in prispevali k njegovim prelomnim odkritjem. Omenil je, da je pomembno biti osredotočen na pomembna vprašanja in vztrajati. »Nisem imel jasne vizije, ko sem leta 1984 začel delati na protitelesih. Okoli leta 1988, ko smo razvili prvo humanizirano protitelo, alemtuzumab, se je spremenil moj pogled na prihodnost protiteles,« je sir Gregory Winter pojasnil svoje začetke.

Sir Gregory je razpravljal o izzivih interdisciplinarnega raziskovanja in pomenu transparentnosti in poštenosti pri sodelovanju. Izpostavil je, kako lahko akademija in industrija bolje sodelujeta, ter ponudil nasvete raziskovalcem, kako premagati prehod od temeljne znanosti do razvoja terapevtikov. Sir Gregory Winter pravi tako: »Koristilo bi, če bi akademiki imeli več izkušenj z industrijo in obratno. Pomembno je, da znanstveniki na obeh straneh lahko neposredno sodelujejo brez dodatne birokracije.« Kot ustanovitelj več biotehnoloških podjetij pravi, da so pomembne tudi poštenost, samokritičnost in sposobnost jasne razlage dela ter predstavitve vizije. »Ne obljubljajte preveč; bodite realistični; morate biti pripravljeni tvegati, vendar je ključna transparentnost glede tveganj; ne skrivajte tveganj pred investitorji in pričakujte trdo delo na dolgi rok,« so misli sira Gregoryja Winterja, ki jih povzemamo iz spodnjega intervjuja. Nazadnje je izpostavil pomembnost praktičnih aplikacij, kot so RNA cepiva in ciljani radiofarmaki, ter potencial umetne inteligence in strojnega učenja v farmacevtskih raziskavah.

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It is a great honour to welcome Sir Gregory Winter, Nobel laureate and one of the most influential figures in biotechnology and pharmaceutical sciences, to this interview. Sir Gregory's ground-breaking work in phage display technology has vastly advanced our understanding of antibody development and its applications in medicine. As a co-founder of Cambridge Antibody Technology, he has pioneered innovations leading to the development of numerous monoclonal antibodies, now essential in the treatment of diseases such as cancer and autoimmune disorders. His contributions have not only transformed modern pharmaceuticals but have also inspired researchers and professionals worldwide.

In this exclusive interview for the readers of the Journal of the Slovenian Pharmaceutical Society, *Pharmaceutical Journal of Slovenia*, we are privileged to have him sharing insights on his work, the evolving role of biotechnology in the pharmaceutical industry, and the importance of interdisciplinary collaboration in research. Thank you, Sir Gregory Winter, for joining us today.

Anja Pišlar (AP): Our readers would love to hear your thoughts on what winning the Nobel Prize means to you personally and how it has influenced your work and perspective on science.

For a scientist, it's the ultimate recognition from your peers, from fellow scientists. But it does come with some drawbacks, as it means I have to be more careful about what I say – people tend to take my words more seriously. I can't be flippant or ironic; it's quite dangerous if I am. In terms of influencing my work, I'm formally retired, so it hasn't really affected my research itself. But it has changed how I spend my time. I receive many invitations to give talks and try to inspire young scientists, which I gladly do when possible. Science has been good to me, so I feel it's important to give back.

Mojca Lunder (ML): You've spent most of your scientific career in Cambridge, a renowned hub of scientific excellence. How did your experiences there shape your research? And how did it ultimately lead to your ground-breaking discoveries in antibody therapeutics?

It was both the experience and the mindset, but my attitude was perhaps the most critical. I saw myself as a kind of medieval apprentice aiming to become a master craftsman, learning cutting-edge techniques and combining them to find novel solutions to important questions. I remember once describing a paper as 'interesting,' and my supervisor replied, '*Interesting be buggered; is it important?*" Rude as it was, it taught me to focus on what truly matters.

My work on developing humanized antibodies required a deep understanding of antibody structure, combined with practical knowledge of advanced recombinant DNA technology of the time. It required both the scholarship and the tools to tackle the right questions.

ML: Were there particular mentors, supervisors, or colleagues who influenced you significantly and helped guide you toward the goals you set for yourself?

Absolutely. As I mentioned, my supervisor encouraged me to tackle important questions, which has been foundational for me. Another mentor, Fred Sanger[1] – who, as you know, won two Nobel Prizes – once gave me a crucial piece of advice when I was struggling with an experiment. He said, '*Most things in our line of work are technical. Do you think it should work?*' I replied, '*Yes, I think it should.*' He told me, '*Well, you just have to fiddle around with it for longer and it probably will work.*' This lesson stuck with me. I've shared it with others over the years because often, it's simply about adjusting conditions—almost like cooking, where changing ingredients or proportions can suddenly yield the right result instead of a mess.

Another mentor, César Milstein[2], also a Nobel Laureate, advised me to work on antibodies rather than enzymes, which was my initial focus. He appreciated my work with enzymes but told me, '*It's such a pity you're working with enzymes. You should really work with antibodies.*' Given that he had some control over my position, I took his advice, and in retrospect, I'm immensely grateful I did. It was an incredibly valuable piece of guidance, and it shaped the course of my career for the better.

[1] **Frederick Sanger** (1918-2013), a British biochemist who received the Nobel Prize in Chemistry twice, in 1958 for his work on the structure of proteins (specifically insulin), and in 1980 (sharing it with Paul Berg and Walter Gilbert) for the development of a DNA sequencing method that is still widely used today

[2] **César Milstein** (1927-2002), an Argentinian biochemist who shared the Nobel Prize in Physiology or Medicine in 1984 with Niels Kaj Jerne and Georges J. F. Köhler for developing the hybridoma technique, that for the first time made it possible to produce monoclonal antibodies

Tomaž Bratkovič (TB): That's a great lead-in to my question. When you first began working on therapeutic antibodies, what was your vision for the future? How do you view the evolution of antibody-based therapies today?

I can't say I had a clear vision for the future when I started working on antibodies in 1984. I thought they might be useful in some clinical applications, but the full extent of their potential only became apparent as the research progressed. It was around 1988, when we developed the first humanized antibody, alemtuzumab[3], that I began to see the possibilities. Alemtuzumab was used in two patients with non-Hodgkin lymphoma, and it effectively destroyed a large mass of tumour cells in the spleen. That was thrilling, and importantly, the antibody wasn't rejected – it was tolerated by the patients. That moment made me realize I should focus more on applications and that the antibody field could indeed become significant. From then on, I saw my future as being closely linked to antibodies, and I believed there were exciting things ahead. Still, I couldn't have imagined they'd become as successful as they are today.

TB: Do you have any thoughts on the evolution of antibody-based therapies with bispecific and trispecific antibodies? Has their development surprised you?

Not at all. From the start, we were working on technologies to create bispecific antibodies, as it was one of the major challenges. César Milstein, in fact, had successfully produced bispecific antibodies many years before by creating what he called 'hybrid hybridomas.' The potential for bispecifics was clear even then; they could bring different cell types together or target two soluble molecules simultaneously. However, I think the pharmaceutical industry has been quite slow to develop them. The concept has been around since the '80s, but it has taken time for industry to move beyond the 'single-flavor' monoclonal antibodies to more complex, 'tutti frutti' antibodies with multiple functionalities.

In some ways, it's akin to combination therapies. Antibodies are often used alongside other drugs, especially in cancer, or with agents like methotrexate in rheumatoid arthritis. With bispecific antibodies, you essentially have a built-in combo therapy in one molecule. This allows for targeting a disease from several angles simultaneously, though it's likely we'll continue to see monoclonals combined with single small-molecule drugs in many cases.

ML: Interdisciplinary research is a cornerstone of many modern pharmaceutical R&D efforts. What do you see as the main challenges in collaborating with experts from different fields to achieve breakthrough discoveries?

First, you need to find someone with the right expertise, and then you need to clarify the ownership of the research and the work product moving forward. Are they simply helping with this project, or is it a genuine collaboration with potential for future joint work, where both parties would have a say in the direction? Being clear about this from the outset is crucial.

Often, people are happy to help with specific expertise or equipment, such as access to a biophysical instrument, without intending to take over your research field. But if you collaborate with someone whose expertise closely aligns with your own, there can be a risk of competing for ownership of the research. So, I think transparency is key. Personally, I haven't encountered many issues in collaborations. I find that treating collaborators fairly goes a long way. Of course, there are times when someone might feel I'm being selfish, or I might feel others have been a bit selfish in their dealings. But overall, I've had positive experiences with most collaborators. The key is to be upfront from the beginning and to try to see things from their perspective as well.

ML: In September at the University of Ljubljana, Faculty of Pharmacy, you delivered a lecture offering your perspective on knowledge transfer from academia to start-ups. Could you share with our readers some of the challenges you encountered, and perhaps suggest ways academia and industry might collaborate more effectively to accelerate new therapy development?

There are certainly challenges, as academia and industry operate in very different cultures. It would be helpful if academics had more exposure to industry, for instance, through a period of consulting or working within a company. Likewise, it would benefit industry scientists to gain

[3] **Alemtuzumab,** a humanized monoclonal antibody (i.e., IgG1 with hypervariable loops from a mouse antibody grafted onto a human IgG framework) directed against DC52, a protein expressed on mature lymphocytes; alemtuzumab was used until 2012 for the treatment of patients with B-cell chronic lymphocytic leukaemia, and is still sometimes used today for the treatment of adults with highly active relapsing-remitting multiple sclerosis.

experience in academia – whether by undertaking a research project or lecturing students on industry and commercialization challenges. These exchanges could foster better understanding and collaboration.
One of the biggest improvements would be if university technology transfer offices didn't monopolize the interface between academia and industry. Scientists on both sides should have the freedom to engage directly without the added layer of bureaucracy.

TB: I know you're not one to give advice, but as someone who has founded multiple biotech companies, what guidance would you offer a researcher looking to bridge the 'valley of death' – the challenging gap between basic science and the development of new therapeutics?
First, you need to present your research and its potential as clearly and simply as possible. Test your ideas with colleagues, and talk to friends in the industry to refine your pitch, whether for start-up funding or a collaboration with an established company. Focus on what you know, and build a team for the rest. Don't try to do everything yourself – it's rare that you'll be able to. You have to learn to delegate and work effectively with a team. Also, avoid overpromising. With start-up funding especially, if you claim you'll achieve something, investors may struggle to evaluate how feasible it really is. They'll certainly conduct due diligence, but they'll hold you to your claims. Over-promising can lead to a major loss of confidence if you don't deliver, especially if you've assured them it would be straightforward. I've found it's better to communicate the vision while being upfront about potential challenges. This may turn some people away, but it's better for them to have a realistic understanding. Lastly, be prepared to work harder than ever. Moving research to market is tough – it often takes years before you see results, and it's not something you can pursue casually. If you're serious, expect to work intensely and consistently for the long haul.

TB: You've mentored many prominent scientists and entrepreneurs. In your experience, what qualities are essential for success in biotech or pharmaceutical research? Persistence, I assume, is one...
Absolutely, persistence is crucial. But I'd also say hard work, deep scholarship, attention to technical detail, focusing on important questions, and immersing yourself fully in the subject. Equally important are honesty, self-criticism, and the ability to explain your work simply and convey your vision to others – selling that vision is essential if you want to succeed. Especially at the biotech and pharmaceutical interface, how you present your work makes a big difference. Sometimes you'll see brilliant researchers with presentations full of complex details, making it impossible to discern their actual goals. They may be geniuses, but they still need to learn how to structure their ideas in clear, connected language. What's obvious to you might not be to others.
Talking to stakeholders and simplifying your message is key. You need a clear vision: how will this make money? Industry partners may admire your technical achievements, but they also want to know where the revenue will come from, how long it will take, and if they'll see returns in their lifetime.

ML: So, would you say that risk-taking is also a necessary quality for someone pursuing this path?
Of course, you've got to take risks. I'd add that you try to minimize those risks by covering as many bases as possible. But it's also crucial to be transparent about the risks with both investors and academic funders. Don't hide it – just be clear. This might affect your funding, but a straightforward approach is best.

AP: Which recent scientific achievements have impressed you the most?
I'd say I'm most impressed by practical applications. Years ago, theoretical advancements interested me deeply, but now I'm drawn to solutions with tangible impacts. The development of RNA vaccines, for instance, was remarkable, and I believe there's still much potential ahead. Another exciting area is targeted radiopharmaceuticals, especially with small peptides. This approach could revolutionize radiotherapy, offering precision targeting that allows us not only to confirm a hit but to use specific isotopes for effective tumour treatment. These areas really stand out to me.

ML: Given this year's Nobel Prize[4], what's your perspective on the role of AI and machine learning in the future of pharmaceutical research, particularly for drug discovery and development?
AlphaFold's ability to predict protein structures is impressive, but it currently offers limited insight into the strengths of interactions between ligands and receptors. To advance

[4] **Nobel Prize in Chemistry in 2024** was jointly awarded to David Baker, Demis Hassabis and John M. Jumper for their work on computational protein design and protein structure prediction.

further, particularly for tasks like improving drugs or predicting binding affinities, we'd need vast datasets. While sequencing data is relatively straightforward to obtain, determining the binding affinities for millions of protein variants isn't.

Machine learning certainly has potential, especially for chemists aiming to enhance drug binding or modify properties. Today, they analyse structures visually; ideally, an AI[5], system should be able to capture this expertise. However, translating that intuitive process into an expert system is challenging. Some pharmaceutical companies certainly find AI useful in developing novel ligands for a specific disease target, but it still leaves open the prediction of their toxicity profiles.

Machine learning can certainly support certain steps in drug development, but not every stage. AI is essentially a compendium of experience, so while it may match human capabilities in some respects, it may not exceed the insight a well-conducted scientific experiment provides. For example, developing high-affinity antibodies with machine learning might be feasible if you have enough data. But there's also the alternative approach we use: mutating antibodies, placing them on phage[6], and selecting based on affinity. This gives billions of leads simultaneously, allowing precise selection based on binding affinities.

AP: Thank you, Sir Gregory, for sharing your insights with us today.

[5] **AI** Artificial Intelligence

[6] **Phage display,** a molecular biology technique based on modification of bacteriophage (i.e., bacterial viruses) genomes in such a way that the coat proteins of assembled virions are fused to foreign proteins or peptides of interest; this enables the display of any (poly)peptide to the external milieu; large collections of peptide or protein variants can be displayed and screened for affinity against a chosen target to select the ones with desired properties (typically high affinity).