Designing mini-antibodies

The development of bicyclic peptides and the exploration of their properties at the Ecole Polytechnique Fédérale de Lausanne reveal their promise as highly effective and robust alternatives to therapeutic antibodies for treating a range of conditions, including cancer.

To begin, what work do you undertake as part of NCCR Chemical Biology?

The consortium consists of more than 20 research groups in Switzerland that work together to address biological questions with chemical tools. My laboratory is providing the bicyclic peptide technology to generate ligands of proteins for study. For example, in collaboration with Professor Freddy Radtke, we are developing selective inhibitors of the Notch signalling pathway. The ligands will be used as research tools and potentially as therapeutics. We benefit greatly from such collaborations, as our partner groups in the Centre provide experience in specific fields, as well as materials such as target proteins, assays and animal models for testing bicyclic peptides.

What inspired you to develop bicyclic peptides?

During my PhD in Professor Dario Neri’s group at the Swiss Federal Institute of Technology in Zurich, I was exposed to the field of therapeutic antibodies. The powerful performance of antibodies as therapeutics impressed me deeply. At the same time, I learned about the limitations associated with their large molecule size. This inspired me to think about smaller molecule formats with similar binding qualities. Polycyclic peptides appeared to be suitable, as the peptide loops could interact with protein targets, much like antibody complementarity-determining regions. Sir Greg Winter, at the Medical Research Council Laboratory of Molecular Biology in Cambridge, and I managed to establish a method of isolating bicyclic peptides with high binding affinities for a range of clinically relevant protease targets.

Can you explain how you generate bicyclic peptides that bind to targets of interest?

In simple words, a pool of billions of different bicyclic peptides is generated – in our laboratory typically around 5x10^9 – and those few bicyclic peptides that bind to a protein of interest are fished out by dipping the protein briefly into the pool, washing it to eliminate peptides not binding tightly and analysing the bound bicyclic peptides. The identification of the isolated bicyclic peptides is enabled by a technology named ‘phage display’. Once the phage peptides are fished out of the pool, DNA in the phage is sequenced and the peptide sequence derived based on the genetic code. As bicyclic peptides cannot readily be displayed on phage, we display linear peptides and cyclise them in a chemical reaction prior to the fishing experiment.

Do you expect your spinoff company Bicycle Therapeutics to be a success?

I have much confidence in the bicyclic peptide technology, as every day I experience in my own laboratory the power of this molecule format. Moreover, Bicycle Therapeutics has an excellent management and research team with a lot of experience in the pharmaceutical industry. Additionally, it has a distinguished board of directors, including Winter. He previously founded the two successful companies CAT and Domantis. His enormous experience and know-how have allowed Bicycle Therapeutics to develop strong therapeutic programmes based on scientific and economic criteria. I hope that these programmes will develop into drugs with many benefits for patients.

**KEY DETERMINANTS OF** the effectiveness of active compounds in new drugs are their capacity to travel through the body to the site of action, their ability to bind biological structures and modulate processes, and their resistance to rapid degradation by biological molecules such as enzymes. Their acceptability is further measured in terms of their side-effects, their means of delivery and how readily they can be manufactured.

Most drugs used today are small chemicals such as acetylsalicylic acid in aspirin. In recent years, a powerful and novel class of molecules – monoclonal antibodies – have entered the clinic. Monoclonal antibodies can bind with high affinity and specificity to virtually any biological structure. They have proved very efficient in the treatment of severe diseases such as cancer and immunological disorders; they can, for example, selectively kill tumour cells by binding to structures on their surface.
The two loops of the bicyclic peptide structure interact with the protein much like antibodies bind to antigens via their surface loops: effectively, they are small, adaptable antibodies.