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Editorial overview: Peptides in cancer

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According to Globocan, in 2018 there were 18.1 million new cancer cases worldwide and 9.6 million cancer deaths, demonstrating the dire need of new therapeutic options for this multifaceted disease. In fact, despite our increasing knowledge of the molecular mechanisms underlying cancer aetiology and maintenance, we still do not possess a sufficient arsenal of therapeutics to modulate all the intracellular and extracellular pathways that contribute to its development and maintenance. Many of those pathways are dependent on so-called 'undruggable' targets, molecules for which the design of inhibitors has been especially challenging so far [1]. Our laboratory is pioneering inhibitory strategies for one of these targets: Myc. Because of its undisputable role in maintaining all transcriptional programs related to tumorigenesis, Myc is a 'most wanted' target in cancer treatment, although, in spite of this, no Myc inhibitor has yet reached the clinic. One of the main reasons is that Myc is an intrinsically disordered protein, devoid of any defined three-dimensional structure in solution and lacking an enzymatic binding pocket, such that standard small molecule approaches struggle to be effective [2]. Novel strategies are therefore being taken in an attempt to achieve important breakthroughs in targeting Myc and other undruggable proteins. Among them, peptides represent a particularly promising strategy to combat many different diseases, including cancer. The functional flexibility of peptides allows them not only to be used when they possess inherent anti-cancer activity, but also in order to stabilize drugs, enhance cellular uptake of other proteins or drugs, enable specific targeting of cancer cells with therapeutic or imaging agents, and even as cancer vaccines. In this context, we have recently demonstrated the pharmacological efficacy of the Omomyc mini-protein (90 amino acids), whose particularly favourable biophysical properties and cell-penetrating capability allow its use as a viable drug against Myc for the treatment of lung cancer and make it an excellent candidate for further clinical development [3].

Peptides have arrived to the clinic much later than small molecules, having to overcome the most common limitations of short plasma half-life and negligible oral bioavailability, but represent now a significant fraction of therapeutics in clinical trials. They include peptides isolated from natural sources, those derived from chemical synthesis (which became feasible in the 1950s) and others that are recombinantly produced. Technical advances in peptide production in particular have led to major improvements in specificity and efficacy, due to a significant change in their length, initially limited to less than 10 amino acids (in the 1980s),

but now encompassing sizes several-fold longer or even mini-proteins of around 100 amino acids.

The peptide drug market worldwide was estimated at US\$21.3 billion in 2018 and is projected to reach US \$46.6 billion in 2024 (<https://www.transparencymarketresearch.com/pressrelease/peptide-therapeutics-market.htm>). There are currently approximately 70 approved peptides and over 150 peptides in active development in the areas of metabolic disease, oncology, and cardiovascular disease [4], with cancer being currently the biggest field for newly approved peptides.

Hence, in this special section, we have focused on peptides used in cancer treatment and gathered the expert opinion of authors from across the globe regarding a range of different topics surrounding these new therapeutics.

Paul Walker's group in Geneva, Switzerland [5] provide us with their view on '*Peptides as cancer vaccines*'. Interestingly, while peptide cancer vaccines currently have a low therapeutic effect – due in part to an immunosuppressive tumour microenvironment – they have huge potential for cancer prevention and treatment. More powerful combinations of adjuvants and immunomodulators should help unleash their full potential as immunooncology treatments.

'*Protein-driven nanomedicines in oncotherapy*' from the groups of **Antonio Villaverde and Esther Vazquez in Barcelona, Spain** [6] focuses on the use of protein-based nanometric structures that can target cancer cells taking advantage of intrinsic cytotoxic activity. They describe a number of possible strategies (summarized in the figure that is the cover page of this special section), that include protein nanocarriers, proteins that stabilize or target drugs to cancer cells, and even self-assembling, self-delivered nanoscale protein drugs.

Drazen Raucher in Mississippi, USA [7] presents us with a specific review on the use of peptides for the treatment of glioblastoma, one of the oncological diseases considered mostly incurable to date. The review is titled '*Tumor Targeting Peptides: Novel Therapeutic Strategies in Glioblastoma*' and discusses the highly specific targeting capacity of peptides as a solution to limit the side effects usually associated to conventional therapies. He also presents a summary of the difficulties (and potential solutions) associated with crossing the blood brain barrier, encountered by peptides in order to achieve therapeutic impact in the brain.

Peptide therapeutics for the treatment of brain tumours and brain metastasis are further discussed by **Daniela Rossi's group in Pavia, Italy** [8], who summarize the last literature on pre-clinical studies validating this approach and focus extensively on peptides in clinical trials, with their respective outcomes, in the review '*Peptides in Clinical Development for the treatment of Brain Tumors*'. While there currently may be only one Phase III trial starting (for brain metastases), other early-phase trials for various brain tumours are showing promise.

Ines Neundorff's group in Cologne, Germany [9] offer their view on '*Recent advances of anti-cancer therapies including the use of cell-penetrating peptides*', discussing the

advantages of CPPs as carriers for intracellular delivery of drugs, DNA, imaging agents and other proteins, as well as the strategies used to increase their specificity, uptake and anti-cancer activity. In this context, the review presents the design of multifunctional CPP-cargo complexes, taking advantage of functionally different elements.

Expanding further on the theme of CPPs and also discussing other proteins that intrinsically possess cell-penetrating properties, **Toni Jauset and Marie-Eve Beaulieu** from Peptomyc in Barcelona, Spain (Jauset and Beaulieu, 2019) discuss ‘*Bioactive cell penetrating peptides and proteins in cancer: a bright future ahead*’. This review includes a useful summary of cell-penetrating molecules that are currently in clinical trials and development and that could constitute a breakthrough for challenging cancer targets. They also discuss the possibility of using chemistry and drug humanization strategies to overcome challenges associated with clinical applications.

Last but not least, the final review in this special section by **Ülo Langel’s group in Tartu, Estonia** [10] discusses ‘*The future of peptides in cancer treatment*’, taking into consideration their use as diagnostic tools, and focusing on the three main areas of their therapeutic use: intrinsic biological activity of the peptide (such as natural protein mimicry), targeting of cancer cells and delivery of drugs.

We sincerely hope the reader will enjoy this special issue and we hopefully look forward to soon expanding on it with reports of the success of therapeutic peptides in the clinical setting, especially in the field of cancer, where their application has only recently made a significant appearance but promises to have a huge impact.

Biographies

Jonathan Whitfield

Dr Jonathan Whitfield is Staff Scientist at the Vall d’Hebron Institute of Oncology (VHIO) in Barcelona, Spain, where he moved in 2011 to help set up and manage the laboratory of Dr Laura Soucek. Before that he worked with Dr Gerard Evan at the University of California, San Francisco (UCSF). He received his PhD from University College London (UCL) while working at Eisai London Research Labs and at the Eisai site in Tsukuba, Japan. His current research work focuses on inhibition of Myc in glioblastoma by the Omomyc mini-protein, looking at its mechanism of action and therapeutic potential.

Laura Soucek

Dr Laura Soucek graduated in Biological Sciences at the University La Sapienza, Rome (Italy) in 1996 and was awarded her PhD in Genetics and Molecular Biology in 2001. She was a postdoctoral fellow and Assistant Researcher in Dr Gerard Evan's laboratory at the University of California San Francisco (UCSF, USA) until 2011. Since then, she has been leading the Mouse Models of Cancer Therapies Laboratory at the Vall d'Hebron Institute of Oncology (VHIO) in Barcelona, Spain, where she is also ICREA Research Professor and Associate Professor at the Universidad Aut6noma de Barcelona (UAB). She is a cancer research expert specialized in Myc inhibition strategies, as well as founder and CEO of Peptomyc S.L., a spin off company that aims at treating cancer with anti-Myc peptides.

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