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Editorial: The boulder peptide symposium 2021 scientific update

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Editorial on the Research Topic
The boulder peptide symposium 2021 scientific update

The Boulder Peptide Symposium provides an annual forum for presentations to advance the cutting-edge discovery and development of peptide therapeutics. This Research Topic of four symposium presentations explores the use of new tools for peptide drug discovery, development, and manufacturing the novel work discussed during the symposia.

The paper by Lev Shapira and collaborators describes the utilization of in-house developed Artificial Intelligence tools to guide virtual screening for discovery of potential inhibitory peptidomimetic macrocycles for the spike/ACE2 complex. The screening focused on three distinct interactions: 1) allosteric spike inhibition, 2) competitive ACE2 inhibition and 3) competitive RBD spike inhibition. The results showed that while all three approaches yielded hits, only the competitive spike inhibition hits reached sufficient potency to serve as leads. The data validated spike RBD as a drug target but also indicated a relationship between peptide size, target specific binding and efficacy.

A complementary article by Aimee E. Mattei and colleagues, describes the application of informatics tools for *in silico* prediction of dominant T cell epitopes within the sequence of a peptide or protein drug candidate. This would serve as a first step for assessing immunogenicity to aid lead candidate selection and drug safety assessment. Immunogenicity is a notoriously difficult adverse effect to de-risk preclinically. Mattei and co-workers developed the EpiMatrix algorithm to screen natural amino acid sequences for peptides that bind HLA. To date, the HLA binding properties of peptides containing unnatural amino acids (UAA) cannot be reliably predicted by existing algorithms. Accordingly, the authors also developed an *in silico* method for modeling the impact of a given UAA on a peptide's likelihood of binding to HLA and, by extension, its immunogenic potential. Their article discusses how HLA binding studies can be used to estimate the binding potentials of commonly encountered UAAs and "correct" *in silico* estimates of binding based on their naturally occurring counterparts.

Bach-Ngan Nguyen and Numaferm colleagues describe the use of a biochemical tool that enhances folding yields of recombinant disulfide-rich peptides and proteins. The authors refer to this class of long-chained polypeptides as "pepteins," which are said to fall in the range of 30–300 amino acids. Previously, manufacturing of sequences of this size has

proven challenging due to problems including mis-folding, aggregation, and resulting low production yields. To circumvent the problems, the authors devised a novel platform named "Numaswitch" consisting of nine amino acid Ca $^{2+}$ binding extension domains with the consensus sequence GGXGXDXUX (X: any amino acid, U: any large hydrophobic amino acid) named "Switchtags." These tags assist in folding the fusion pepteins into the correct disulfide configuration. Following the folding step, the switchtags are cleaved with Numaferm's Numacut TEV protease. This approach was validated through the successful preparation of an antimicrobial fusion peptide, two antibody fragments and human epidermal growth factor (hEGF).

The final paper by Robin Polt and coworkers describes the application of glycosylation as a viable strategy for enhancing the performance of peptide drug candidates by improving their PK properties, their stability, and their blood-brain barrier (BBB) permeability. The last property is particularly relevant in the case of peptide drugs designed to treat CNS conditions such as Parkinson's disease or traumatic brain injury. The authors performed extensive structure-activity studies on glycosylated pituitary adenylate cyclase-activating polypeptide (PACAP). Results obtained from stability studies both *in vitro* and *in vivo* indicate that their glycosylated lead peptide analogs were more robust than their non-glycosylated counterparts, with disaccharide-containing glycopeptides exhibiting superior stability compared to glycopeptides containing only a single glucose residue. More importantly, their optimized glycosylated peptides demonstrated efficacy in animal models.

In summary, all four articles showcase development of novel tools for improving peptide therapeutic discovery and development. The Boulder Peptide Foundation was established to further the science and knowledge of peptide technology to develop novel therapeutics, biomaterials, medical diagnostics, and other beneficial uses for mankind. As part of this goal, the foundation offers several programs in addition to the annual Boulder Peptide Symposium to support career advancement, seminars, and educational events. These four articles highlight our mission to expand the applications of peptide science.

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Conflict of interest

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