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Abstract

Structural Composition Analysis of Approved Peptide Therapeutics and Diagnostics as a Guide For Future Peptide Drug Candidates

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Abstract: Since the approval of the first peptide therapeutic agent, the 51-amino acid (AA) hormone insulin, in 1923, drug discovery has progressively expanded into the chemical space between small molecules and large proteins. Subsequently, a significant number of peptides (and peptidomimetics) have received regulatory approval, reaching over 100 approved and marketed peptides in 2020. However, unlike small-molecule drugs, there is no general set of guidelines for designing a successful peptide-based drug and this makes the peptide chemists' job of designing future peptide drug candidates challenging. We have performed a detailed structural analysis on the approved peptide therapeutics and diagnostics, providing an overview of their key compositional trends to help guide the design of future peptide medicines. In detail, molar mass distribution, amino acid frequency, peptide modifications, macrocycles, N- and C-termini, origin of peptide design, and polar/lipophilic contribution of each member present in a given approved peptide have been investigated. Over a total of 105 peptide pharmaceuticals analysed, 86% are natural or naturally-derived. Moreover, a bimodal distribution of peptide molar mass has emerged, with the large majority 2000 g/mol. Among all the peptide constitutional members, most (around 81%) are represented by natural L-amino acids, while the residual 19% comprises non-natural AAs and modifications. A balance between polar and hydrophobic residues have been found within the peptide structures. Finally, 46% of the approved peptides are cyclic and 5 to 7 members cycles are the most common. The data collected have been made freely available on PepTherDia (http://peptherdia.herokuapp.com), an online open-source database. Forecasting a starring role for peptides in the coming decades, we anticipate that new clear trends and, perhaps, rules in structural composition will emerge beyond our observations, leading to improved rational peptide drug design.