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Oxidation, aggregation and immunogenicity of therapeutic proteins

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STELLINGEN

Behorende bij het proefschrift

Oxidation, Aggregation and Immunogenicity of Therapeutic Proteins

1. Oxidation of aromatic amino acid residues not only can induce covalent protein aggregation, but also may lead to cross-links between protein molecules and amino acids, which are typically present during cell culture and are often used as formulation excipients. (*This thesis*)
2. Micromolar concentrations of TETA, in comparison with other potential anti-oxidants, effectively inhibit copper catalyzed protein oxidation, aggregation and fragmentation. (*This thesis*)
3. IFN α -2a, IFN α -2b, IFN β -1a and IgG1, oxidized and aggregated with the oxidative system Cu²⁺/ascorbate, induce anti-drug antibodies (ADAs) in immune tolerant mice. (*This thesis*)
4. Immune tolerance in mice can be circumvented by administering them particulate forms of insulin, such as insulin covalently bound to 50 nm polystyrene nanoparticles and, insulin aggregates created by oxidation. (*This thesis*)
5. By the action of performic acid it is possible to split insulin into its separate polypeptide chains by conversion of the cysteine to cysteic acid residues. (F. Sanger. *Biochem. J.* **1949**, *44*, 126–128)
6. Especially in the ascorbate system, a reaction between a tyrosyl radical and oxygen is more likely than that of two tyrosyl radicals. (Y. Kato et al. *Free Radic. Biol. Med.* **2001**, *31*, 624-32)

7. Transgenic mice with tissue-specific expression of the human insulin gene in the beta cells of the pancreas do not produce insulin-specific antibodies when injected with human insulin. Tolerant transgenic mice injected with human or porcine insulin reflect the clinical situation. When injected with bovine insulin the transgenic mice produce antibodies. (J. L. Ottesen et al. *Diabetologia* **1994**, *37*, 1178-1185)
8. Protein therapeutics have increased dramatically in number and frequency of use since the introduction of the first recombinant protein therapeutic, human insulin, 25 years ago. Protein therapeutics already have a significant role in almost every field of medicine, but this role is still only in its infancy. (B. Leader et al. *Nat. Rev. Drug. Discov.* **2008**, *7*, 21-39)
9. Şayet bir gün çaresiz kalırsanız bir kurtarıcı beklemeyiniz. Kurtarıcı kendiniz olunuz. (Should you be desperate one day, do not wait for a leader to save you. Instead be the leader yourself) (*Mustafa Kemal Atatürk*)
10. Meer en meer blijkt, dat de tegenwoordige constitutiefomules niet in staat zijn enkele isomerie gevallen te verklaren. (It is more and more evident that the actual constitutional formulas are not able to explain some cases of isomerism) (*Jacobus Henricus van 't Hoff*)
11. To myself I am only a child playing on the beach, while vast oceans of truth lie undiscovered before me. (*Isaac Newton*)
12. Felix qui potuit rerum cognoscere causas. (Happy is who is able to discover the cause of things) (*Publio Virgilio Marone*)

Riccardo Torosantucci