



Faculty of Science
CHARLES UNIVERSITY

Department of
ORGANIC CHEMISTRY

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Subject: Bachelor's Thesis Report

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Reviewer: Jiří Míšek, Ph.D.

Thesis Title: Functional Screening of *de Novo* Proteins

The submitted thesis reviews the recent development in so-called *de novo* proteins. Looking for non-native proteins with new structures and new functions is a longstanding goal that was met with only limited success for a long time. However, recent advances show interesting directions to approach this goal. Therefore, this thesis represents a valuable act that summarizes a breadth of literature that recently emerged. The thesis compares mainly two areas. First are the new developments in the rational and computational design and related directed evolution experiments in preparing new proteins with new functions. The second part covers the functional potential of random or non-coding genomic sequences. Naturally, given the vast sequence space of even short peptidic sequences, the occurrence of functions is quite rare but existent, as it has been recently demonstrated. The author does not mention the recent progress in protein structure and protein-protein interaction predictions with machine learning approaches such as AlphaFold and others. These approaches will surely have a major impact on the design of *de novo* proteins and, therefore should be mentioned at least in part devoted to structure predictions of amino acid sequences. The second comment is on missing page numbers.

Apart from these minor shortcomings, the thesis is well written in good English, and it is clear that the author is well versed with the topic. Thus, I recommend the thesis for the defense.

Question: It has been more than twenty years since Keefe and Szostak selected a functional ATP-binding protein from a random-sequence library using mRNA display. Despite the initial optimism, there have not been many other functional proteins selected by this approach. Can you comment on that?

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