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Promotionsverfahren von **Herrn M.Sc. Johannes Ptok**
Auslage der Dissertation und Gutachten sowie Termin der mündlichen Prüfung
Anlage: Einseitige Zusammenfassung der Dissertation

Sehr geehrte Damen und Herren,

in dem oben genannten Promotionsverfahren wird die Annahme der Dissertation

Modellierung des Spleißergebnisses durch Kombination von 5'ss Stärke und spleißregulierenden Elementen

von den Berichterstattenden Prof. Dr. H. Schaal, Prof. Dr. M. Feldbrügge und Prof. Dr. E. Steinmann beantragt. Sie kann zusammen mit den Gutachten in der Zeit

vom 02.05.2024 bis 13.05.2024

eingesehen werden. Bitte wenden Sie sich zur Einsicht an das Promotionsbüro (promotionmnf@hhu.de).

Einsprüche gegen diese Dissertation können nur zwei Tage nach der vorgenannten Frist geltend gemacht werden. Erfolgt kein Einspruch, so gilt die Dissertation als angenommen (§ 7 Ziffer (5) PO).

Sofern die Dissertation angenommen wird, findet die mündliche Prüfung am

16.05.2024 um 10:00 Uhr

im **Raum 22.21.U1.012** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Prof. Dr. J. Frunzke, Prof. Dr. J. Altschmied und Prof. Dr. S. Scheu.

Die Öffentlichkeit ist bei der Befragung zugelassen.

Mit freundlichen Grüßen
im Auftrag

Dissertation Johannes Ptok - Summary

Pre-mRNA splicing is an mRNA processing step in which intronic sequences are excised and exonic sequences are ligated. Variations in splice site selection, so-called alternative splicing, enables expression of different proteins, originating from the same pre-mRNA transcript. Initially, an RNA duplex is formed between the 5' splice site (5'ss) and the free 5' end of the U1 snRNA. Splicing regulatory elements (SREs) recruit splicing regulatory proteins (SRPs), like hnRNP or SR proteins, that can greatly influence 5'ss usage, depending on their position. Mutations affecting these regulatory elements can lead to aberrant splicing, which can induce several diseases. Thus, any algorithm that estimates only intrinsic splice site strength is insufficient to correctly capture the impact of mutations on splice site selection, and thus whether they potentially lead to a reduction in functional protein. Publication I reviewed the influence of SREs on 5'ss selection and predictive algorithms, like the HEXplorer. The Splice Site HEXplorer Weight summarizes the overall enhancing or repressing properties of the immediate sequence context of splice sites. Studying 5'ss usage competition between neighbouring 5'ss of a large RNA-seq data set of fibroblasts in Publication II showed, that the differences in HBS and SSHW had to be considered together, to best model predicted 5'ss usage. Intrinsic strength, however, had a greater impact on 5'ss recognition than the SSHW, which was also shown for most likely non-pathogenic mutations of healthy individuals of the 1000 Genome project (unpublished paper I). For fast analysis of sequence variations in context of splicing, the VarCon algorithm was developed in Publication III, which converts ambiguous positional information to genomic positions. To analyze why cardiovascular endothelial cells treated with high concentrations of low-density lipoprotein show low levels of functional NO-synthase 3 (NOS3) protein and high oxidative stress, alternative NOS3 splicing was studied in Publication IV. However, not miss-splicing, but an internal promotor most likely resulted in the truncated NOS3 protein, finally inducing apoptosis. The first 20 amino acids of the Apurinic/Apyrimidinic Endodeoxyribonuclease 1 (APEX1), were able to reduce stress-induced apoptosis in endothelial cells, via upregulation of SELENOT as described in Publication V. To manipulate the SSHW of 5'ss in reporter systems or expression vectors, the ModCon algorithm was developed in Publication VI, which applies a genetic algorithm to manipulate SRP binding via synonymous substitutions. Changes in SRP composition of RNAs, however, might also affect process like RNA export, as observed in Publication VII, analyzing export repressing viral sequence elements, that preferably recruited hnRNP proteins.