Research Staff:

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RESEARCH INTERESTS

- Protein structure
- Sequence-structure relationships
- Dynamics of protein structure
- Molecular dynamics simulations
- Conformational preferences of amino-acid repeats
- Protein-protein interactions
- Kinases
- Intrinsically disordered proteins

RESEARCH ACTIVITIES:

Our research activities include *in silico* structural studies of proteins aiming at elucidating sequence-structure-function relationships under physiological and/or pathological conditions. Emphasis is on amino-acid repeat containing proteins and their role in protein-protein interactions and on proteins mainly related to diseases towards an in-depth understanding of the atomic details of their function. The approach currently used includes techniques, such as homology modelling and molecular dynamics (MD) simulations, including specialized analyses of protein MD trajectories.

RECENT RESEARCH HIGHLIGHTS:

Background & Summary

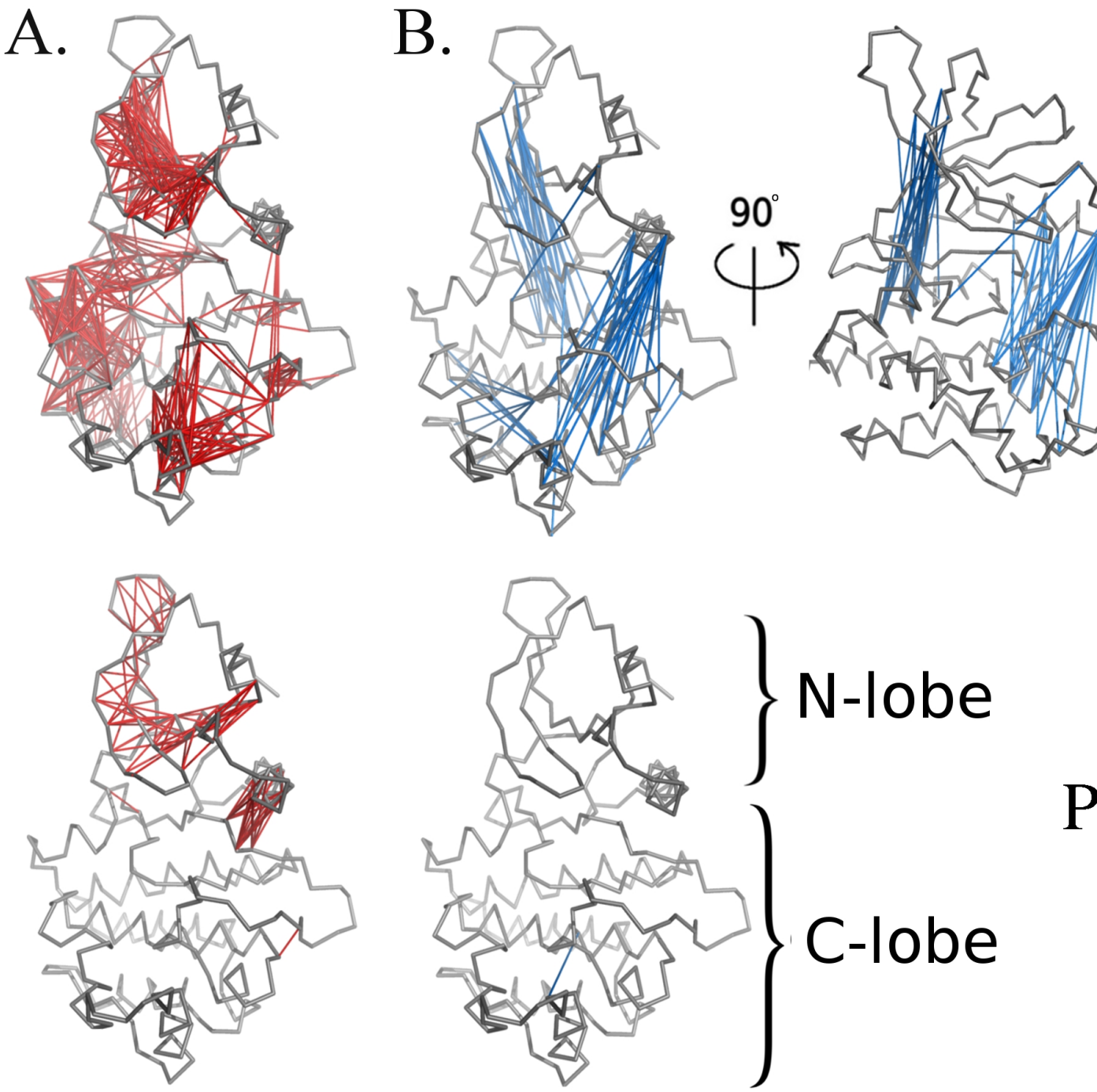
It is now well established that proteins are not static but rather dynamic molecules and that structural flexibility is essential to protein function. However, studying the structure and dynamics of proteins experimentally, is time consuming and in some cases even prohibitive. *In silico*
techniques, such as homology modeling and especially MD simulations, offer a very powerful alternative tool. In the lab we have used such techniques to address various issues related to protein structure-function relationships. For example, we have used
in silico
techniques to elucidate the conformation of highly disordered amino-acid repeats serving as general protein-protein interaction modules (see below), as well as to study the structure of proteins linked to diseases (e.g. kinases) aiming at understanding the atomic details of their function and/or to predict the consequences of gene alterations, including gene mutations linked to diseases:

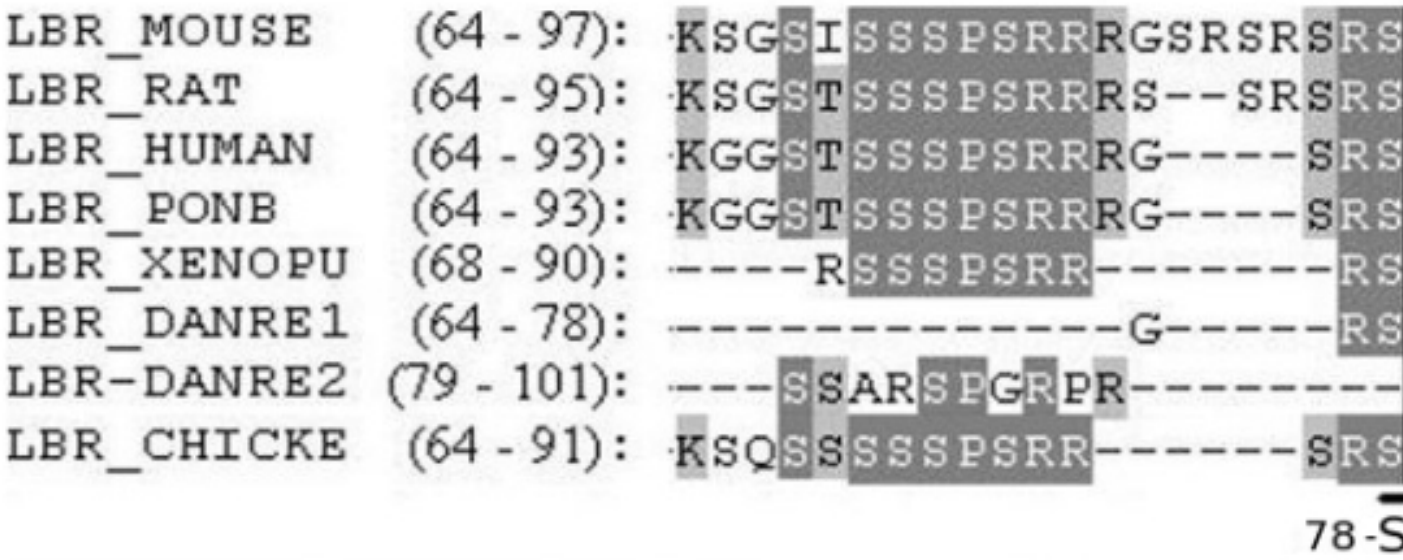
1. ***A. Proteins linked to diseases:***

- ***Tyk2 kinase:***

The non-receptor tyrosine kinase 2 (Tyk2), encoded by the *TYK2* gene, is involved in signal transduction in response to various cytokines as part of the STAT signaling pathway and is associated with the pathogenesis of several diseases, including several autoimmune and inflammatory diseases. A single nucleotide polymorphism of the
TYK2
gene
(rs34536443)
, resulting in a Pro to Ala substitution at amino-acid position 1104 of the resulting protein (
P1104A
), has been found to confer protection against

autoimmune diseases
. However, the atomic details of the protective mechanism remain unclear. To elucidate the structural and functional consequences of this amino-acid alteration, we employed multiple, independent all-atom solvated MD simulations (3 x 100ns each) and explored the structure and dynamics of the catalytic domains of both the wild type Tyk2 and P1104A variant, in their apo-forms. Comparative analyses of the MD trajectories including, monitoring of geometric parameters, hallmarks of the kinase activation state, as well as principal component and cross correlation analyses (
Figure 1
), revealed that this amino-acid change has long-range effects that restrict the dynamics of the resulting protein in favor of inactive conformations. This work is in line with the notion that reduced Tyk2 activity confers protection against autoimmune diseases and added to knowledge in support of the idea of targeting Tyk2 and its pathways as a therapeutic approach against these diseases (More details in
Lesgidou et al, Bioinformatics 2018
).


A.
B.
90°
N-lobe
C-lobe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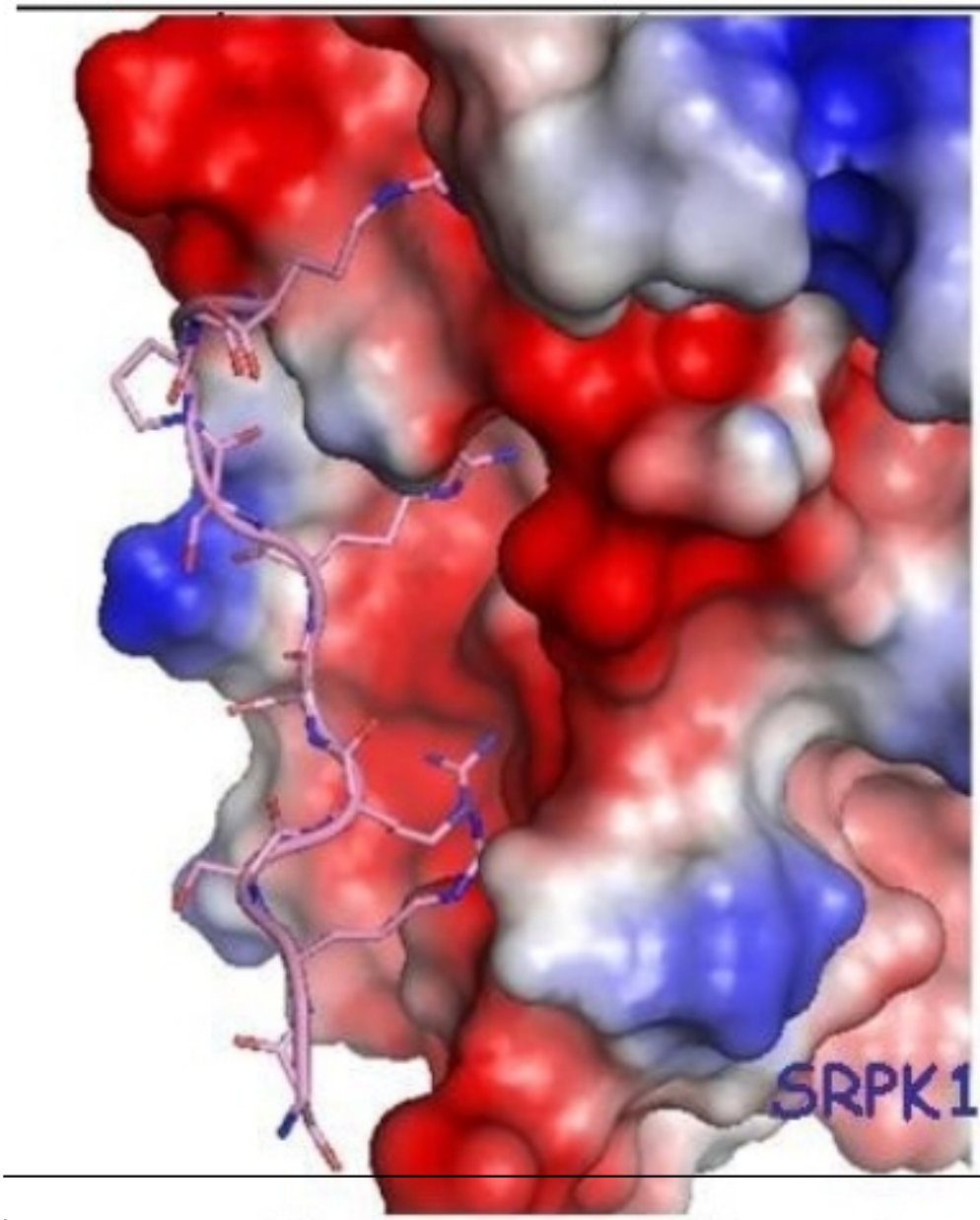
LBR_RAT (64 - 95): KSGSTSSSPSRRRS--SRSRS
LBR_HUMAN (64 - 93): KGGSTSSSPSRRRG----SRS
LBR_PONB (64 - 93): KGGSTSSSPSRRRG----SRS
LBR_XENOPU (68 - 90): -----RSSSPSRR-------RS
LBR_DANRE1 (64 - 78): ----------G-----RS
LBR-DANRE2 (79 - 101): ---SSARSPGRPR---------
LBR_CHICKE (64 - 91): KSQSSSSSPSRR------SRS
78-S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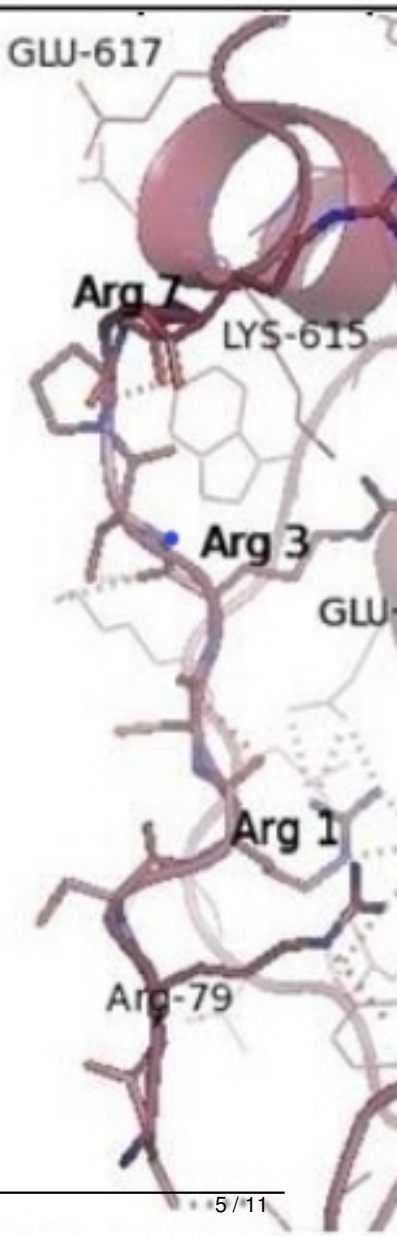
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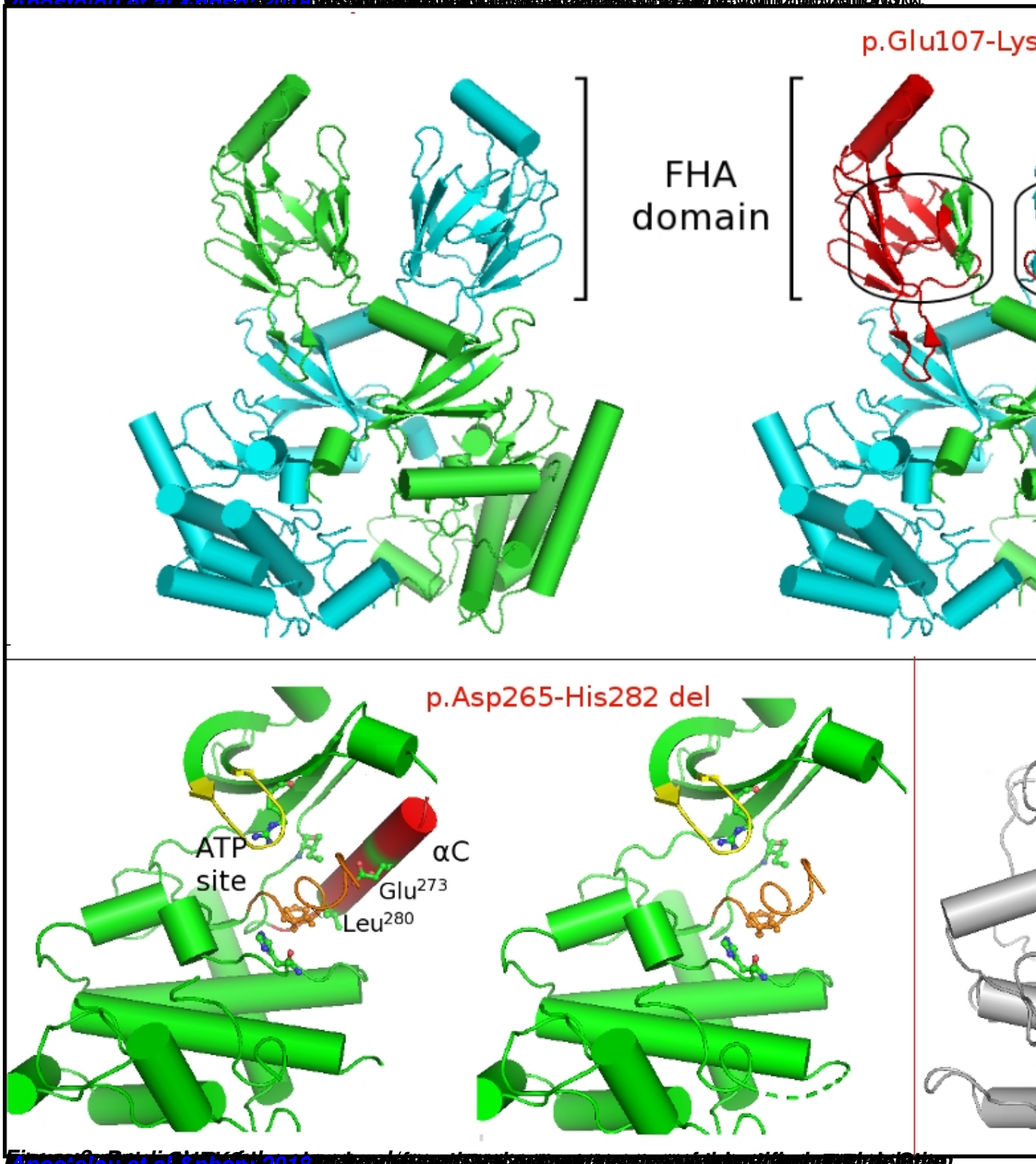
Arg 7
LYS-615
Arg 3
GLU
Arg 1
Arg-79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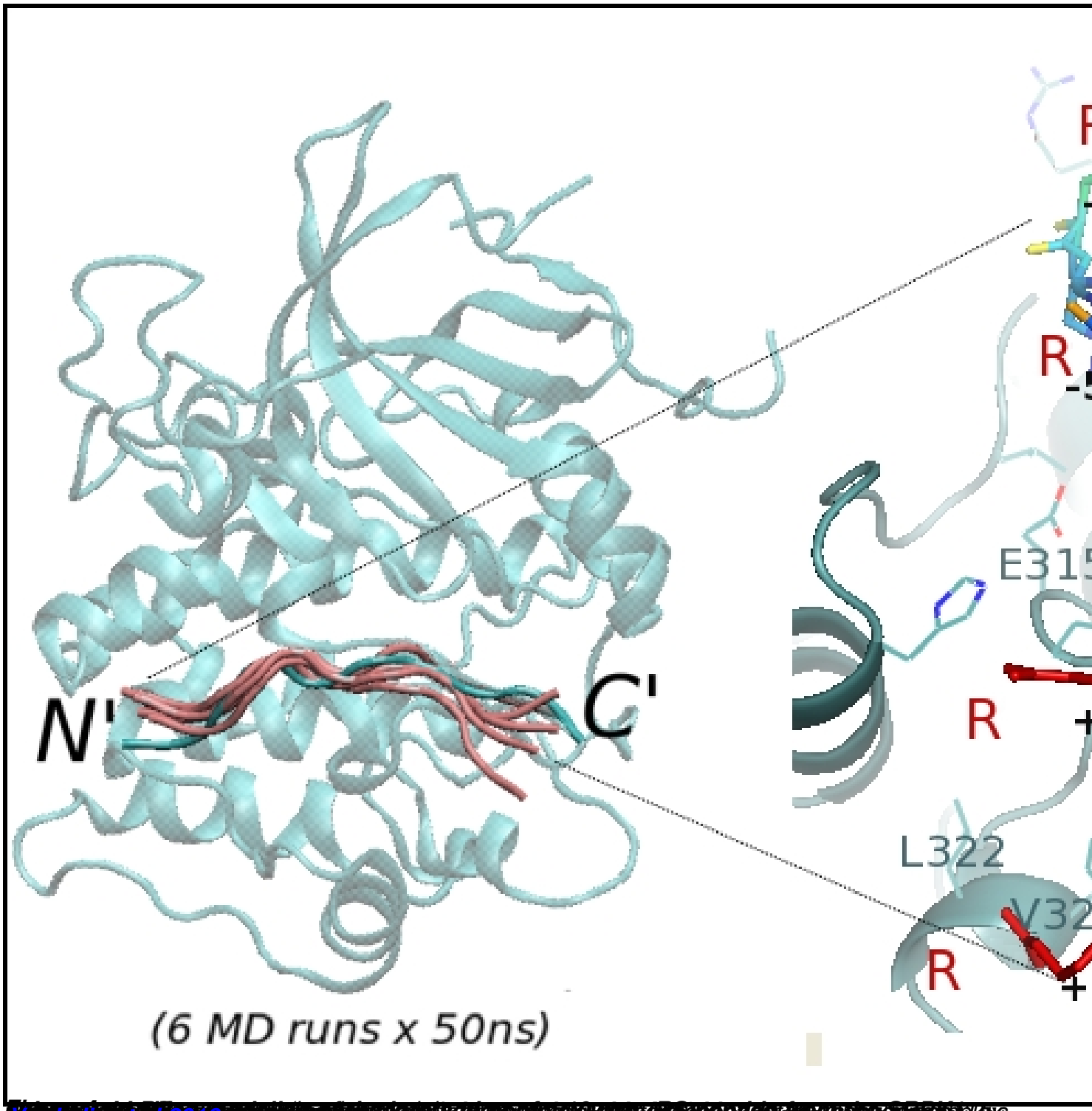
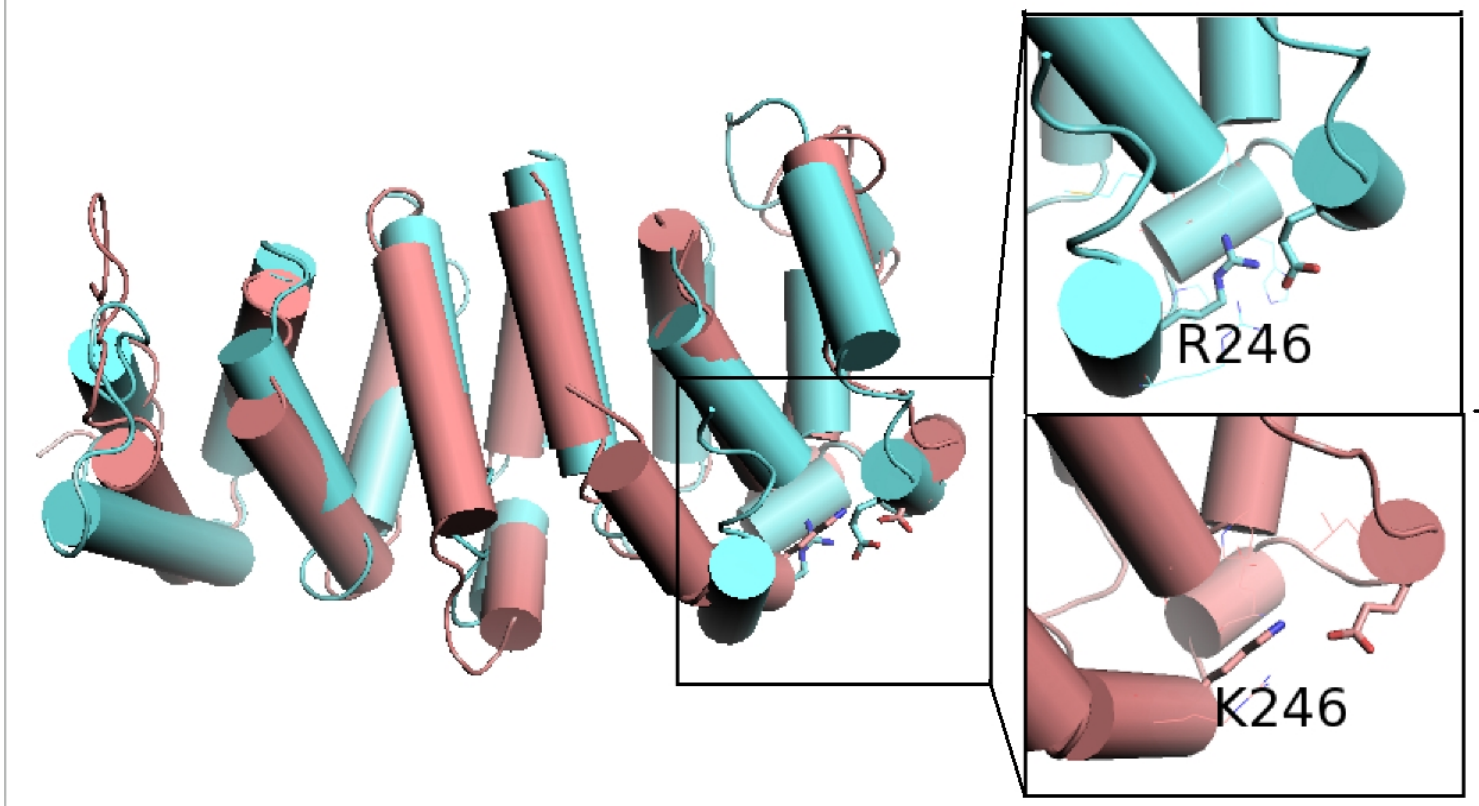
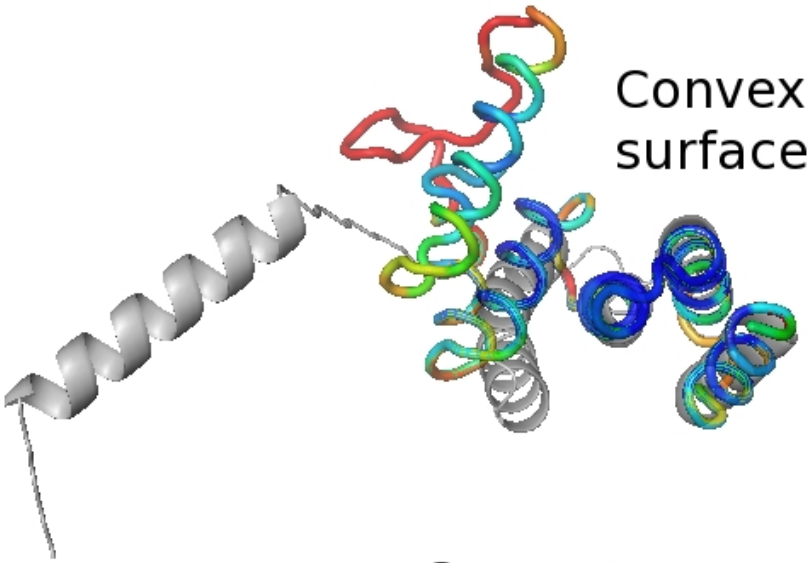
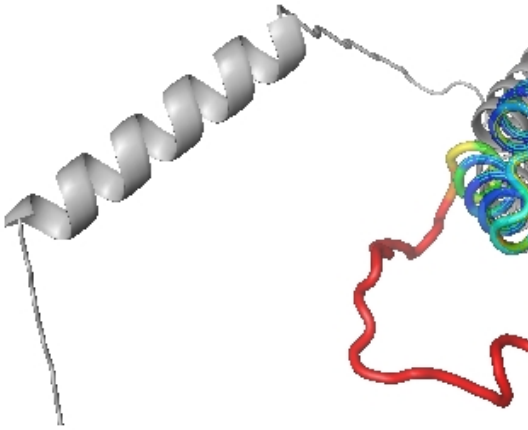
FHA
domain
p.Asp265-His282 del
ATP
site
αC
Glu273
Leu280

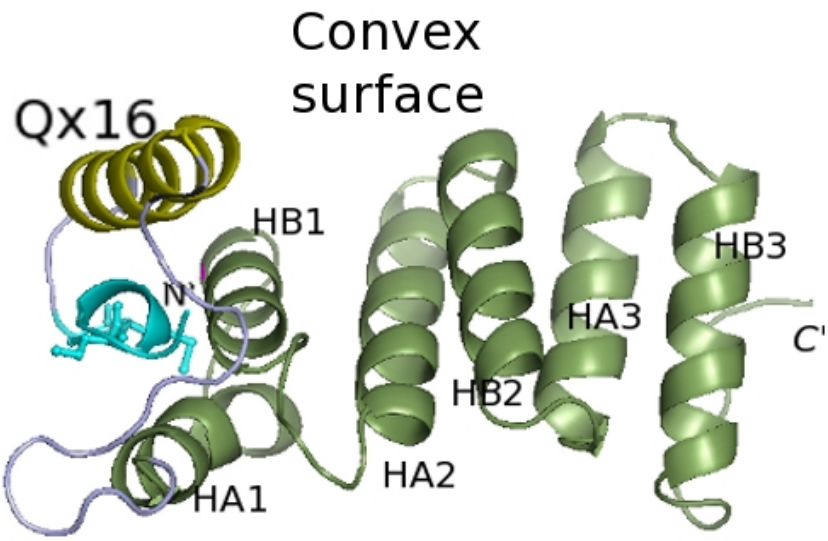


Voukalis et al 2016
Aygeris et al., 2017


R246
K246


Convex
surface




Convex
surface
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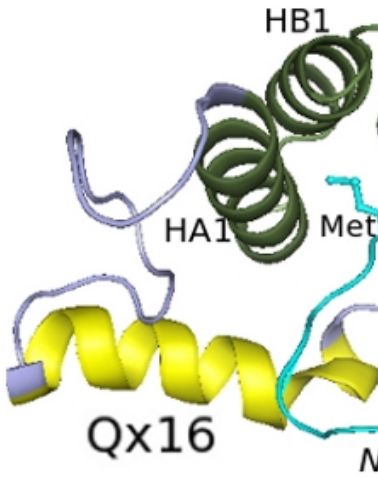
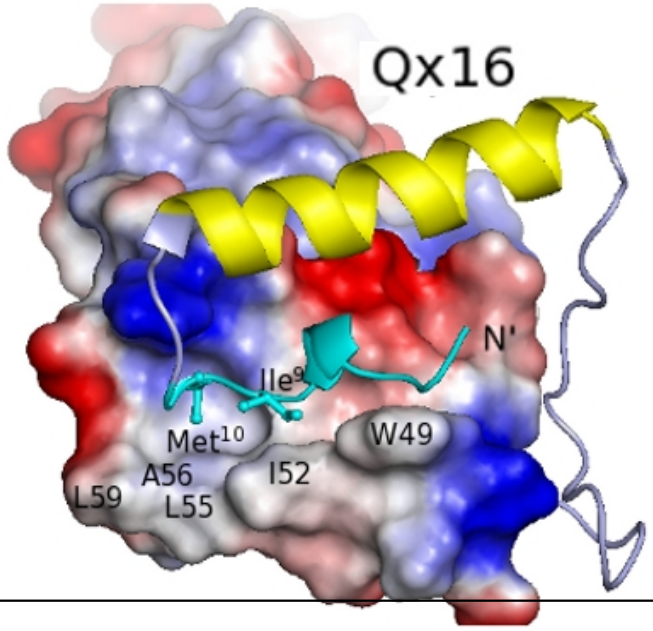
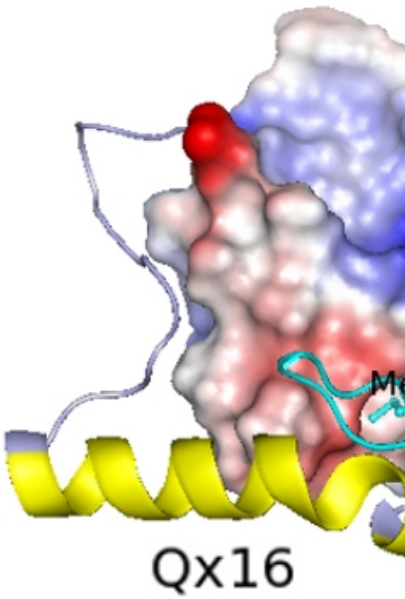
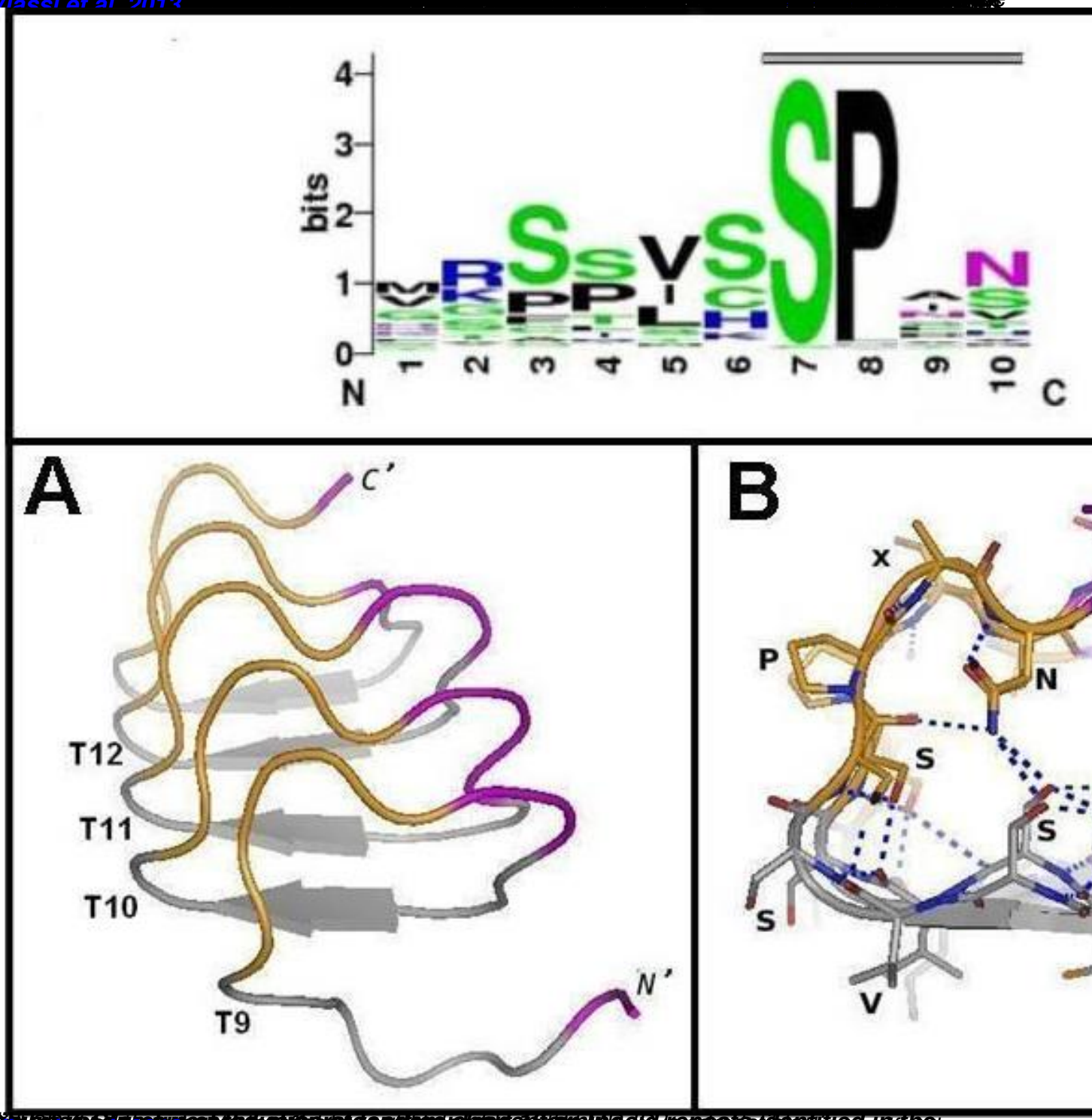
HB1
N'
HB3
HA3
C'
HB2
HA2
HA1


HB1
HA1
Met
Qx16


Qx16
N'
Ile9
Met10
W49
A56
I52
L59
L55


Qx16


bits
4
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4
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7
8
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C'
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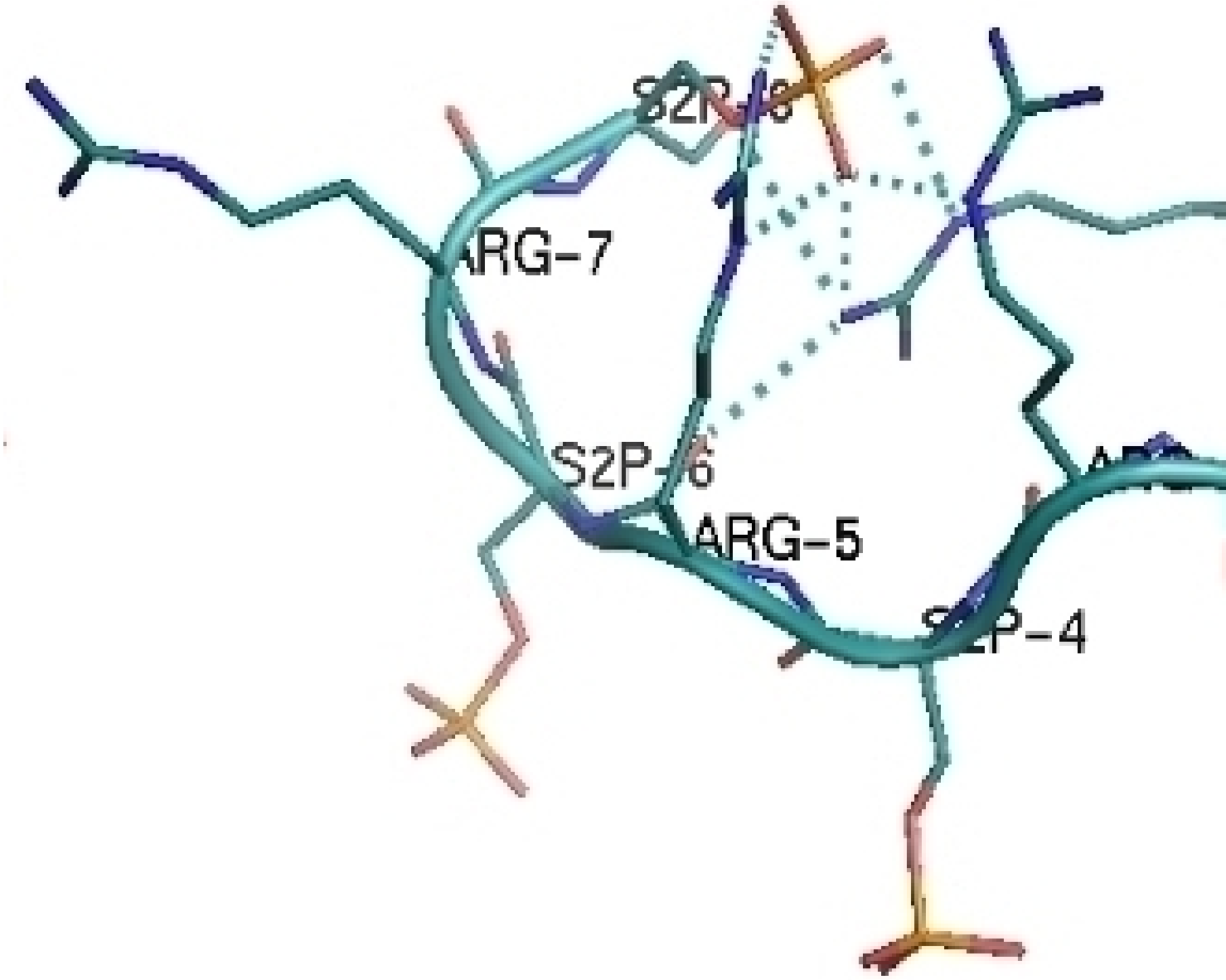
T11
T10
T9
N'
B
x
P
N
S
S
S
V


ARG-7
S2P-6
ARG-5