

Helical assemblies

The School of Theoretical Modeling

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Discussion topics

- Helical assemblies of organelles: inflammasome, proteasome, apoptosome, spliceosome, intasome ...
- Helical assemblies in cancers
- Ankyrin repeats for biofuels
- Designed ankyrin repeats (DARPs)
- Ankyrin repeats for crystallization
- Structure Modeling. Anks1a, Anks1b, Hace1, Anka , and Shank3. Preliminary structures.
- Candidate proteins: GIT1 and GIT2 ...
- How to apply structure modeling in biomedical research
- Methods

Helical assemblies of inflammasome

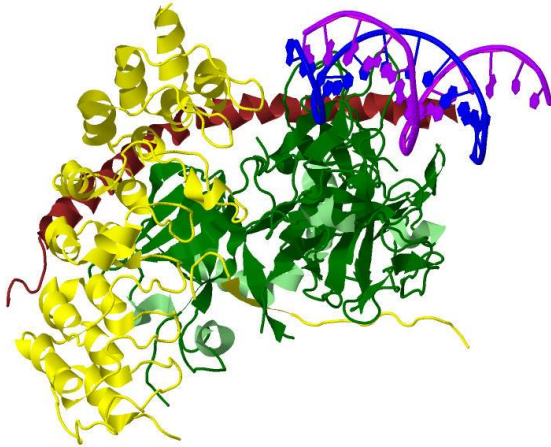


Jmol

Leucine rich repeats domain, LRR, and nucleotide binding domain, NBD, are major components of inflammasome assembly. This nucleated polymerization process with involvement of ATP contributes to our understanding of enzyme activation.

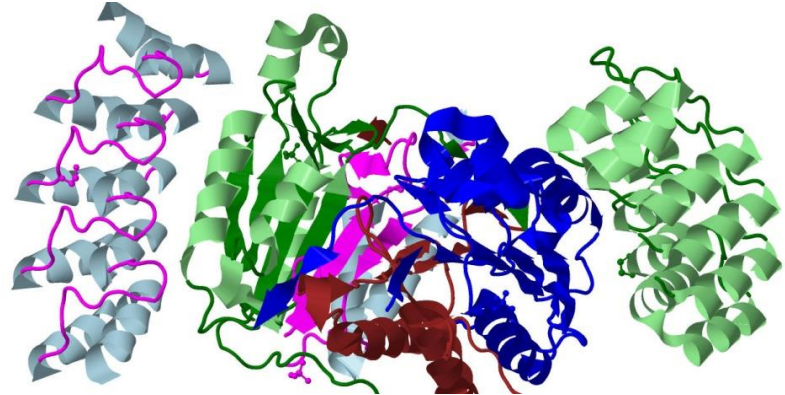
<http://www.sciencemag.org/content/350/6259/404>

Helical assemblies in cancer signaling pathways



Designed protein scaffolds:
Caspase-specific ankyrin
repeats of Darpin /2y11/

Notch receptor ankyrin repeat
domain is important for Notch-
mediated signal transduction
/1ot8 2fo1/



Jmol

<http://www.ncbi.nlm.nih.gov/pubmed/26369833>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3389544/pdf/gmb-35-2-538.pdf>

<http://www.ncbi.nlm.nih.gov/pubmed/22888305>

<http://www.pnas.org/content/105/52/20677.long>

<http://www.jbc.org/content/289/41/28363.long>

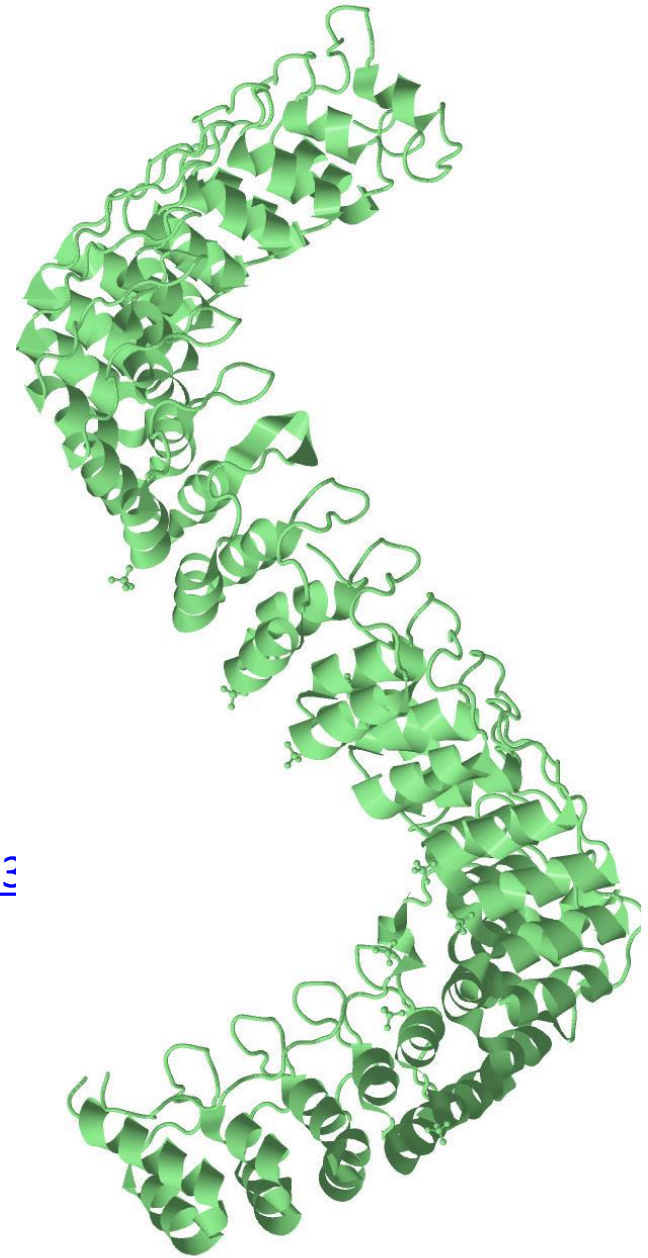
<http://www.jbc.org/content/276/7/4932.long>

<http://www.sciencedirect.com/science/article/pii/S0955067412001019>

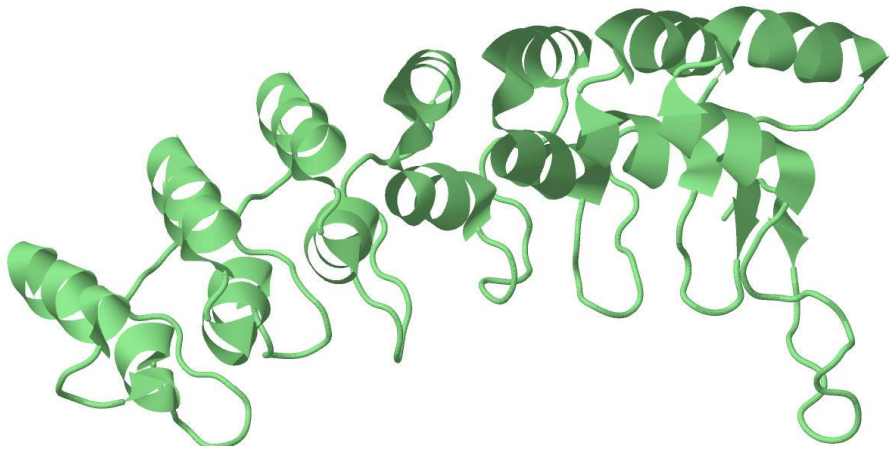
<http://jcs.biologists.org/content/126/2/393.long>

Ankyrins

- Scaffold proteins
- Connect membrane (ion channels, receptors, cell adhesion molecules) and cytoskeleton (spectrin) proteins
- Target proteins to plasma membrane
- <https://www.ncbi.nlm.nih.gov/pubmed/26517892>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC43583>
- <https://www.ncbi.nlm.nih.gov/pubmed/25562645>
- <https://www.ncbi.nlm.nih.gov/pubmed/26517898>
- <https://www.ncbi.nlm.nih.gov/pubmed/11551174>
- <https://www.ncbi.nlm.nih.gov/pubmed/27857066>
- <https://www.ncbi.nlm.nih.gov/pubmed/7919799>



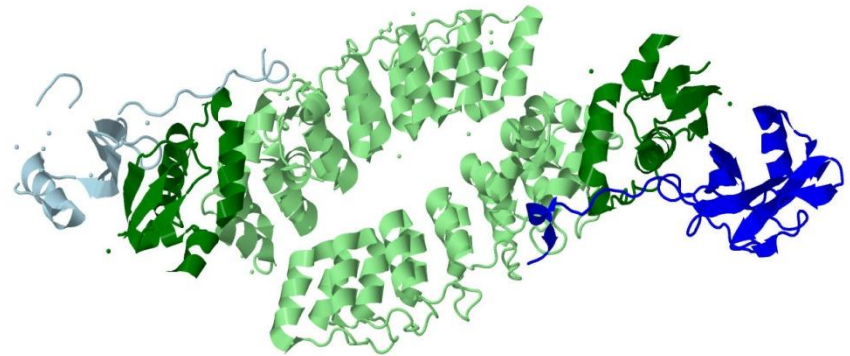
Ankyrin repeats helical assemblies in breast cancer



Jmol

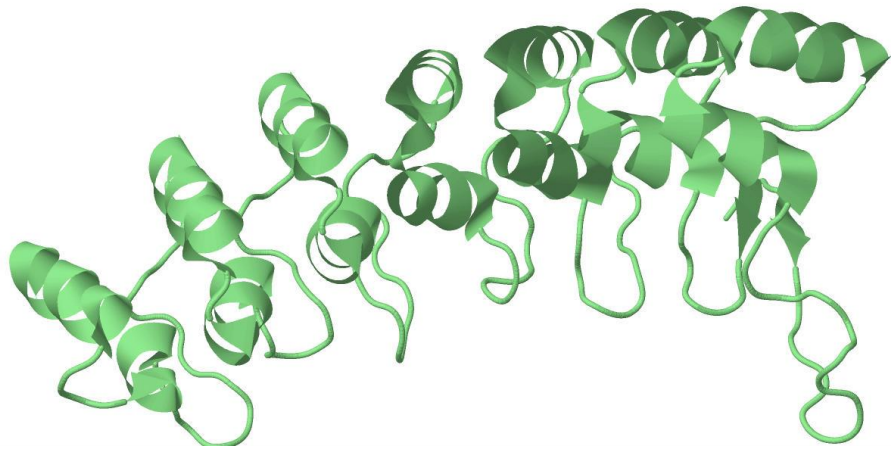
<http://www.ncbi.nlm.nih.gov/pubmed/25961455>
<http://www.ncbi.nlm.nih.gov/pubmed/25882604>
<http://www.ncbi.nlm.nih.gov/pubmed/25860145>
<http://www.ncbi.nlm.nih.gov/pubmed/25848723>
<http://www.ncbi.nlm.nih.gov/pubmed/25391547>
<http://www.ncbi.nlm.nih.gov/pubmed/24778018>

P53 tumor suppressor binds to the ankyrin repeat domain of 53BP2 and gankyrin /Pdb 1uoh 1ycs/
Factor inhibiting hypoxia-inducible factor: hydroxylation within Notch ankyrin repeats domain /Pdb 1ot8 1yyh 2qc9/



Jmol

Ankyrin repeats proteins involved in colorectal cancer



Jmo

Human ankyrin repeat and SOCS-box protein 9 (ASB9) /PDB 3d9h/
and its complex with ELONGINB /PDB 3zng/

ASB9 is used as a prognostic marker of colorectal cancer

<http://www.ncbi.nlm.nih.gov/pubmed/23718802>

<http://www.ncbi.nlm.nih.gov/pubmed/22863622>

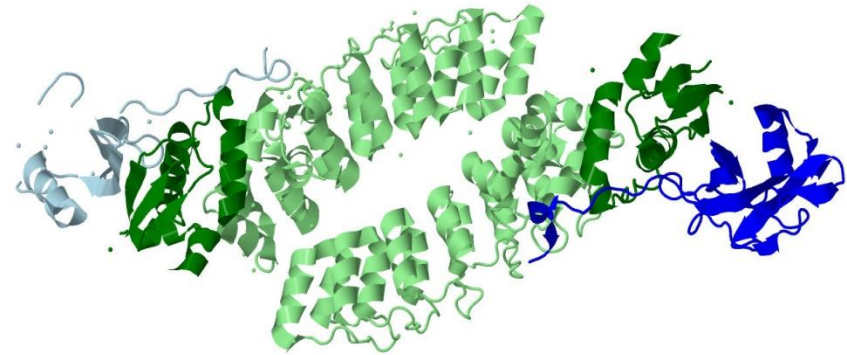
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<http://www.ncbi.nlm.nih.gov/pubmed/18422656>

<http://www.ncbi.nlm.nih.gov/pubmed/9231152>

<http://www.ncbi.nlm.nih.gov/pubmed/8921253>

<http://www.ncbi.nlm.nih.gov/pubmed/8479756>



Jmol

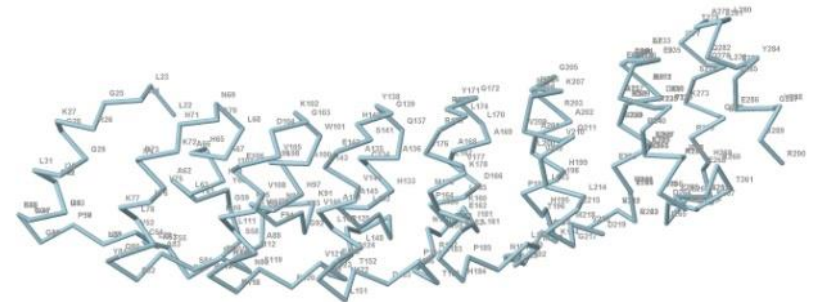
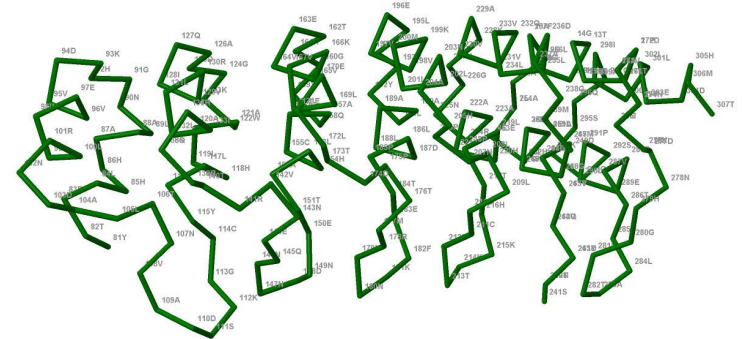
New Topics in Protein Modeling: Preliminary Structures

Anks1a in colorectal cancer cells is Src family kinase substrate and links EGFR, PDGFR, EphA8 to downstream signaling cascade:

<https://www.ncbi.nlm.nih.gov/pubmed/18844995> Ankyrin repeats domain of Anks1a is important for assembly of signaling complexes

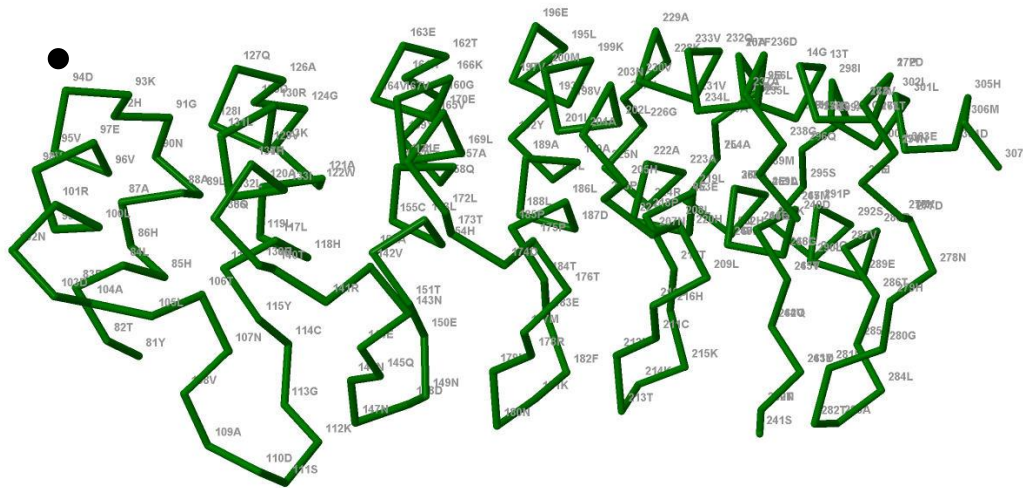
Anks1b binds Krit1 via PTB domain. KRIT1 interactions contribute to Anks1b endothelial permeability:
<http://www.ncbi.nlm.nih.gov/pubmed/?term=26458359>

Ankyrin repeats of Anks1a and Anks1b



Ankyrin repeats domain of Anks1a

preliminary structural model



Anks1a and Anks1b
Structure Modeling
Structure similarities and
dissimilarities

What do we know about Anks1a? Adaptor protein, mediator of assembly of multiprotein complexes, interacts with CD2AP, SH3KBP1, CAPZB, VAPA, ARHGAP10, and other proteins; in colorectal cancer cells is Src family kinase substrate and links EGFR, PDGFR, EphA8 to downstream signaling cascade.

<http://www.ncbi.nlm.nih.gov/pubmed/26698571>

<http://www.ncbi.nlm.nih.gov/pubmed/21081186>

<https://www.ncbi.nlm.nih.gov/pubmed/18844995>

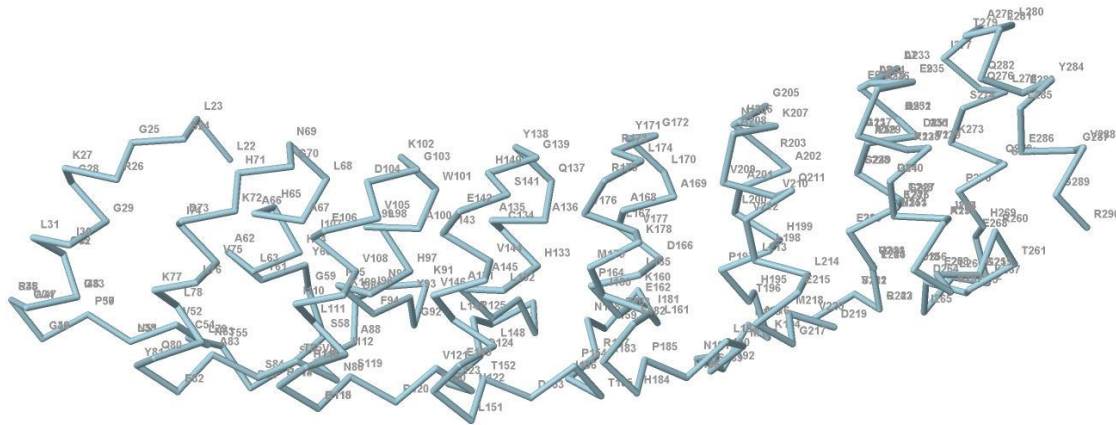
<http://www.ncbi.nlm.nih.gov/pubmed/23144319>

Protein Modeling Course:

<https://plus.google.com/112350944952908623485/posts/R5yj3TszP9r>

Ankyrin repeats domain of Anks1b

preliminary structural model



Anks1a and Anks1b
Structure Modeling
Structure similarities and
dissimilarities

Jmol

Anks1b is major component of postsynaptic density where its phosphorylation by CAMKII mediates molecular reorganization. Interactions of Anks1b with KRIT1 affect endothelial permeability. Anks1b is involved in regulation of subunit composition of NMDA receptor/synaptic plasticity, renal carcinoma, and other processes.

<https://www.ncbi.nlm.nih.gov/pubmed/27477489>

<https://www.ncbi.nlm.nih.gov/pubmed/26698571>

<https://www.ncbi.nlm.nih.gov/pubmed/26085624>

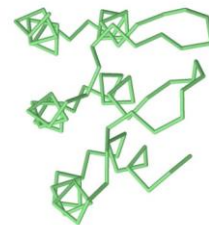
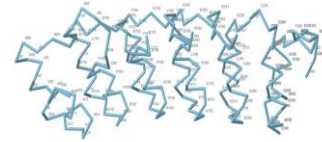
<https://www.ncbi.nlm.nih.gov/pubmed/24479813>

Protein Modeling Course:

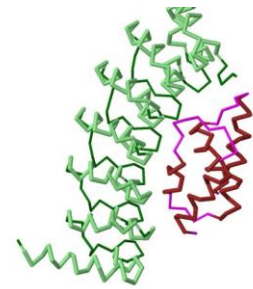
<https://plus.google.com/112350944952908623485/posts/R5yj3TszP9r>

Structure modeling/Structure determination: Candidate proteins

- Tumor suppressor HACE1 (HECT and ankyrin containing protein)
<https://www.ncbi.nlm.nih.gov/pubmed/27805249>
- Variations in NYBR1 gene, including those in ankyrin repeats, contribute to cancer
<https://www.ncbi.nlm.nih.gov/pubmed/27863482>
- Sequence of high similarity to ankyrin repeat in Lysozyme-like protein LYZL5
<https://www.ncbi.nlm.nih.gov/pubmed/27832206>
- Anka
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4132484/>



New Topics in Protein Modeling



Structure of helical assemblies

New methods for predictive modeling

Structural models of new proteins

Webinars

Register www.schtm.org

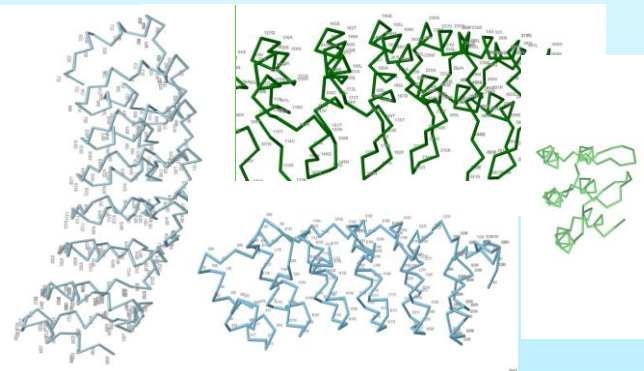
Ankyrin repeats domains of Anks1a, Anis1b, Hace1, and Anka

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4132484>



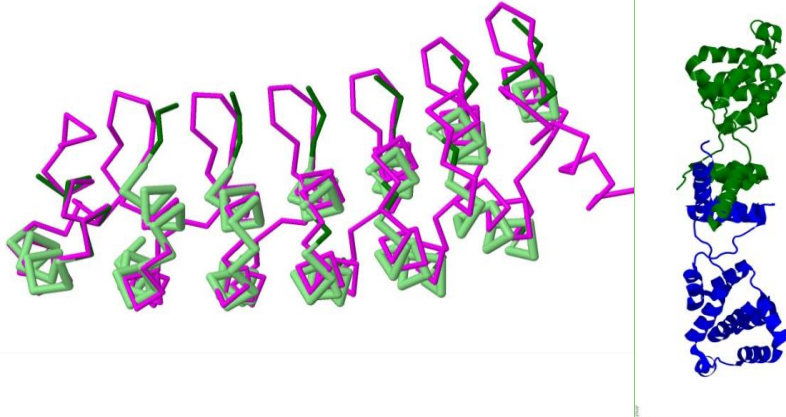
Candidate Proteins: GIT1, ARF GTPase-activating protein.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4829007>

Bring your protein for discussion

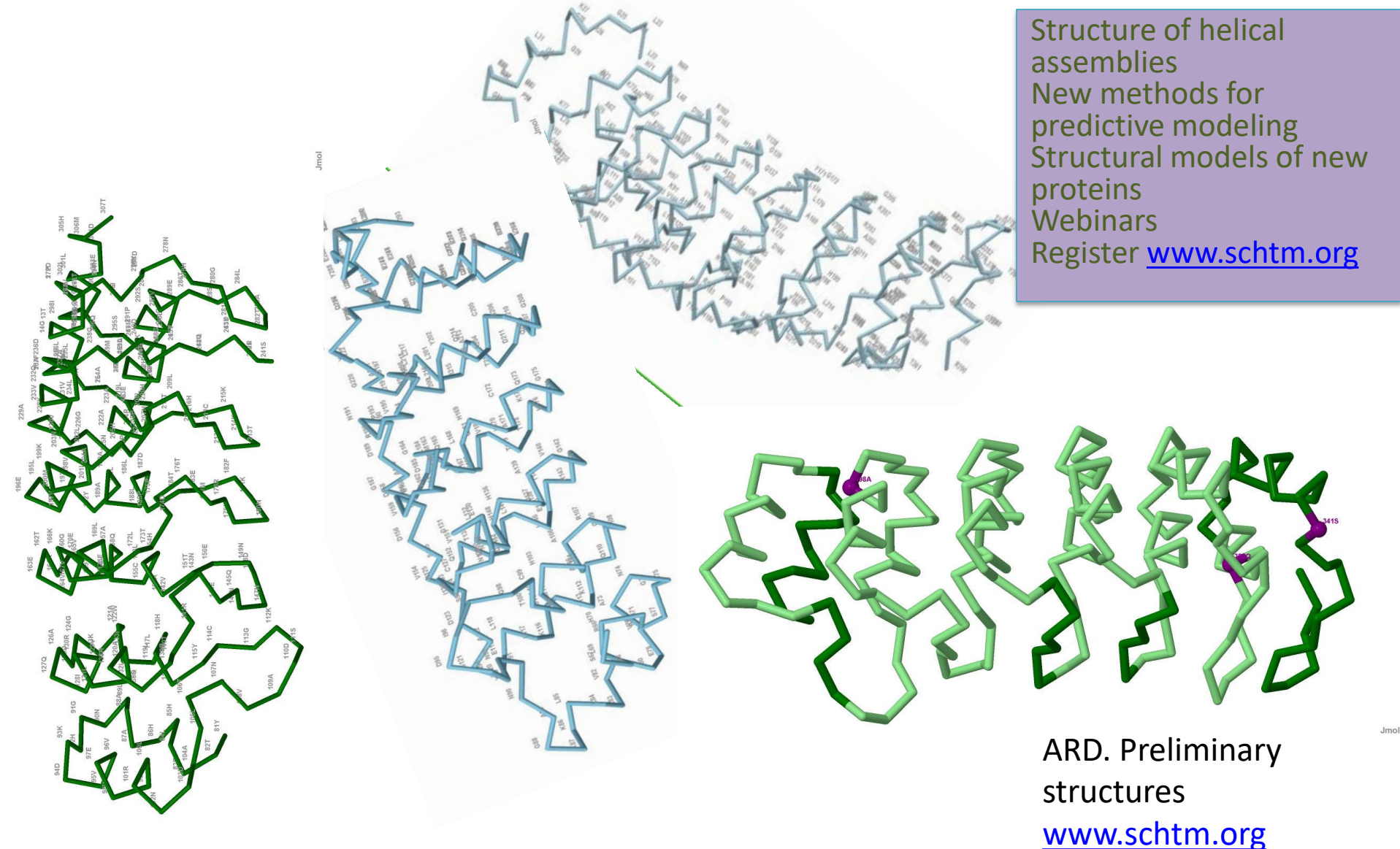
Take a look at our past webinars

<http://www.schtm.org/images/WebinarHelicalAssemblies.pdf>



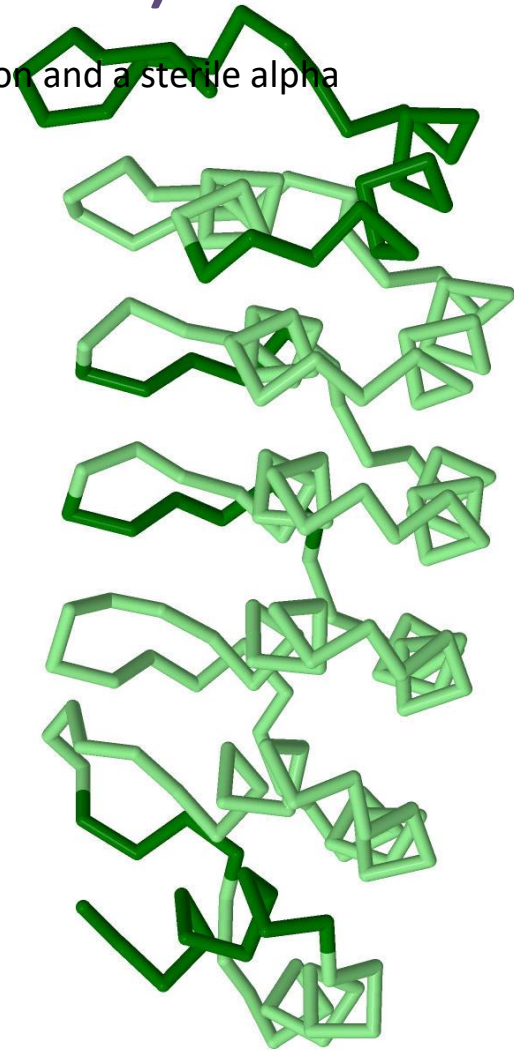
New Topics in Protein Modeling: Preliminary Structures

Structure of helical
assemblies
New methods for
predictive modeling
Structural models of new
proteins
Webinars
Register www.schtm.org



SH3 and multiple ankyrin repeat domains protein 3 (SHANK3)

- Shank3 contains ankyrin repeats, SH3 and PDZ domains, a proline-rich region and a sterile alpha motif (SAM)
- Mutations in Ankyrin repeats domain are associated with autism
<https://www.ncbi.nlm.nih.gov/pubmed/23897824>
<https://www.ncbi.nlm.nih.gov/pubmed/27271042>
- Circuit-specific synaptic transmission involves SHANK3 proteins
<https://www.ncbi.nlm.nih.gov/pubmed/28002633>
- Shank proteins (Ankyrin+SH3) play role in synaptic plasticity
<https://www.ncbi.nlm.nih.gov/pubmed/27795858>
- Shank is a component of PSD assembly
<https://www.ncbi.nlm.nih.gov/pubmed/?term=16439662>
- Shankopathies
<https://www.ncbi.nlm.nih.gov/pubmed/27795858>



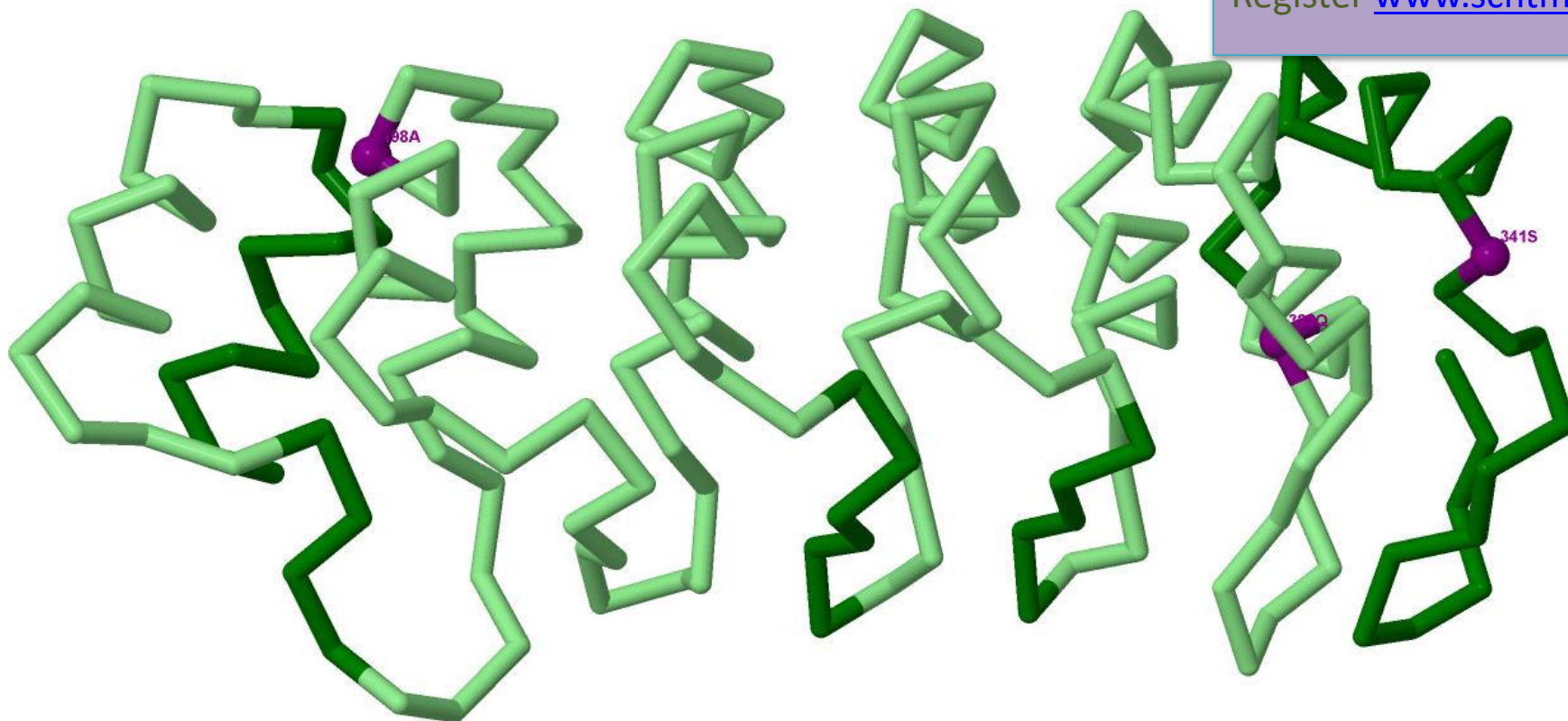
Preliminary structure

New Topics in Protein Modeling

SH3 and multiple ankyrin repeat domains protein 3 (SHANK3)

- Mutations in Ankyrin repeats domain associated with autism
<https://www.ncbi.nlm.nih.gov/pubmed/23897824>
mapped on ARD structure:

Structure of helical
assemblies
New methods for
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New Topics in Protein Modeling

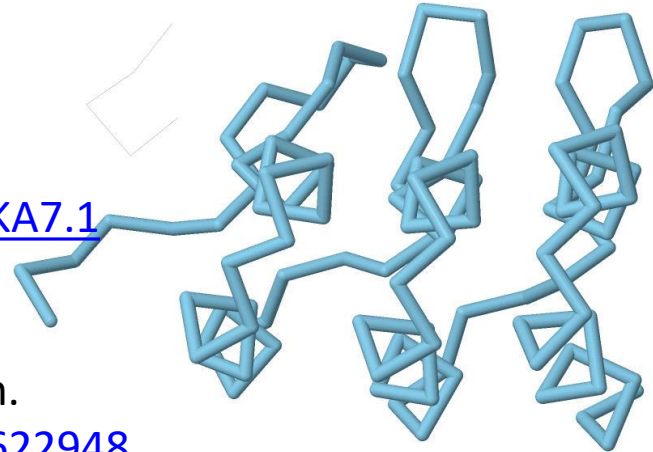
Ankyrin repeat protein Smlt3054

- Ankyrin repeat protein Smlt3054, unique to *Stenotrophomonas maltophilia*, may be key to its pathogenicity

<https://www.ncbi.nlm.nih.gov/protein/B2FKA7.1>

- Implications in Cystic Fibrosis and other diseases. Interactions with F-actin.

<https://www.ncbi.nlm.nih.gov/pubmed/27622948>



ARD. Preliminary structure

www.schtm.org

- *Stenotrophomonas maltophilia* Genome

Crossman, L. C., Gould, V. C., Dow, J. M., Vernikos, G. S., Okazaki, A., Sebahia, M., ... Avison, M. B. (2008). The complete genome, comparative and functional analysis of *Stenotrophomonas maltophilia* reveals an organism heavily shielded by drug resistance determinants. *Genome Biology*, 9(4), R74. <http://doi.org/10.1186/gb-2008-9-4-r74>

Darpins

- Designed Ankyrin Repeats proteins in immunotherapy

<http://www.ncbi.nlm.nih.gov/pubmed/26673402>

Protein Modeling/Structure determination: Candidate proteins

- Nrarp: Ankyrin repeats protein that is evolutionarily conserved transcriptional target of the Notch signaling pathway and function as adaptor protein that brings protein complexes together via protein-protein interactions:
<http://www.ncbi.nlm.nih.gov/pubmed/11783997>
- <http://www.ncbi.nlm.nih.gov/protein/AAH48088.1>

Structure modeling/Structure determination: Candidate proteins

- Cancer-testis antigens are considered to be promising candidates as cancer biomarkers and vaccines. Cancer-testis antigens POTE (POTE Ankyrin domain family http://www.ncbi.nlm.nih.gov/nucore/NM_001083538) are implicated in many cancers: breast, colon, prostate, ovary, and pancreas tumorigenesis as well as non-small-cell lung cancer (<http://www.ncbi.nlm.nih.gov/pubmed/25860145>).
- As helical assemblies of many Ankyrin repeats proteins, POTE gene family members play an important role in cytoskeletal structure development and apoptosis pathways.

Structure modeling/Structure determination: Candidate proteins

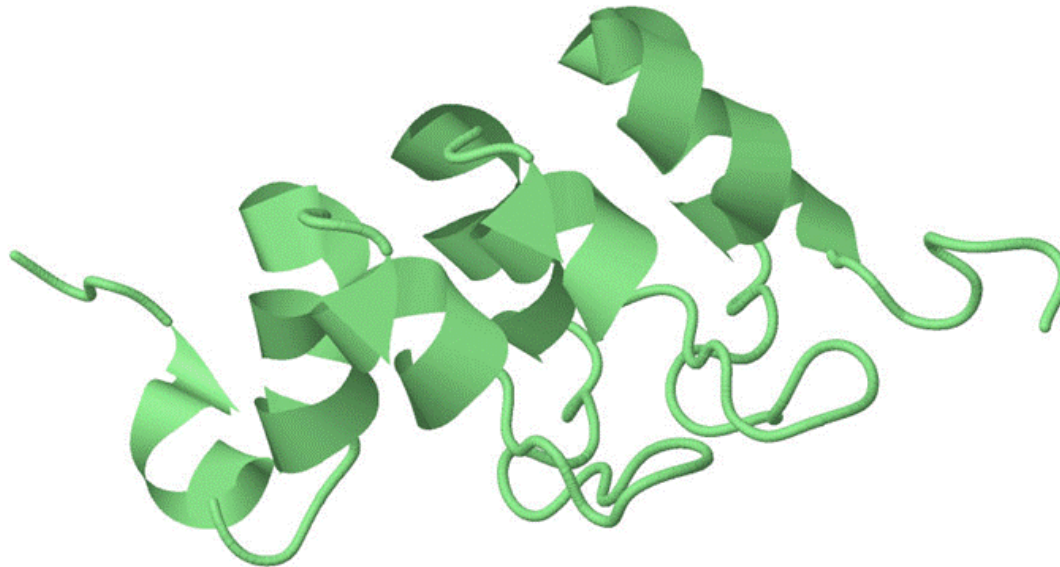
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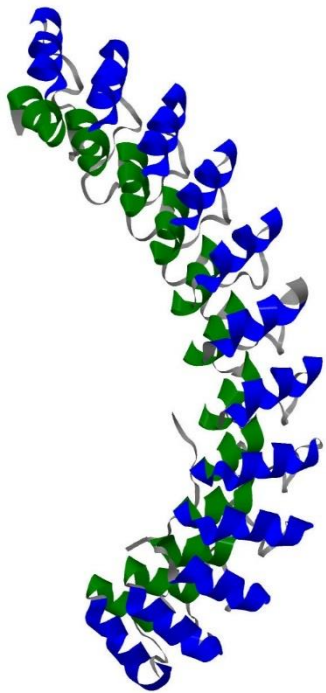
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- ARF GTPase-activating protein Git1 <https://www.ncbi.nlm.nih.gov/pubmed/16598076>
- Git1 and Git2 <https://www.ncbi.nlm.nih.gov/pubmed/16598076>

Ankyrin repeats for biofuels

Eva S. Cunha, Christine L. Hatem, Doug Barrick (2013) Insertion of Endocellulase Catalytic Domains into Thermostable Consensus Ankyrin Scaffolds: Effects on Stability and Cellulolytic Activity. *Applied and Environmental Microbiology* 79: 6684–6696



Protein Modeling/Structure determination. Candidate proteins.



- Publications/Methods:

http://www.springer.com/gp/book/9783319200972?wt_mc=internal.event.1.SEM.BookAuthorCongrat

<http://www.ncbi.nlm.nih.gov/pubmed/25613414>

<http://www.ncbi.nlm.nih.gov/pubmed/21620863>

<http://www.ncbi.nlm.nih.gov/pubmed/20202472>

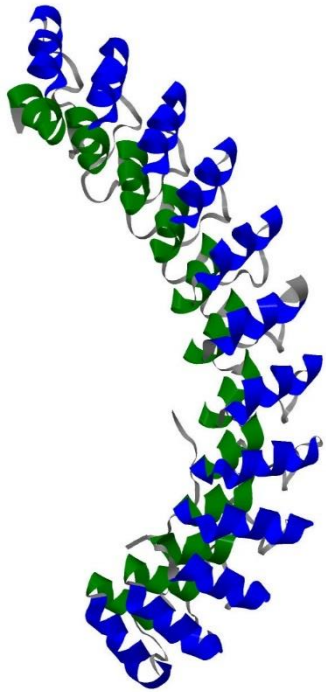
<http://www.ncbi.nlm.nih.gov/pubmed/18786547>

<http://www.ncbi.nlm.nih.gov/pubmed/17379252>

Webinars

Registration: www.schtm.org

Summary of methods



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Chirality of helix interactions determines direction of the assembly

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Orientation of helices affects ligand binding

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Involvement of helical edges is key to the type of the fold

<http://www.ncbi.nlm.nih.gov/pubmed/20202472>

Specific amino acid combinations of helix interfaces are recognition units

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Various types of specific pockets exhibit specific amino acid combinations (viewed in coordinate system of the layer)

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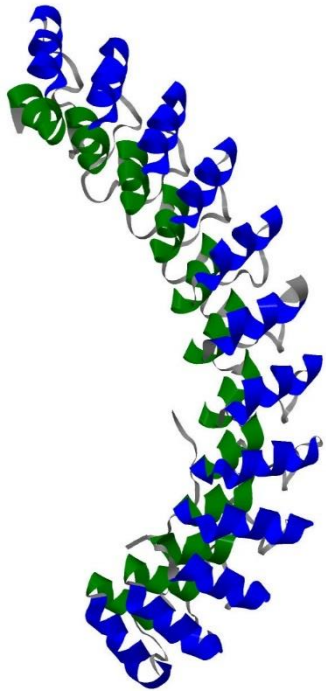
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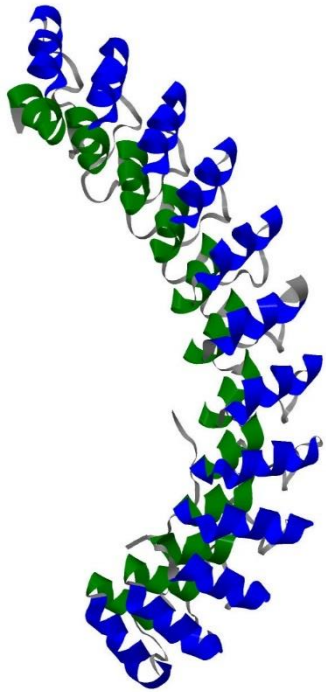
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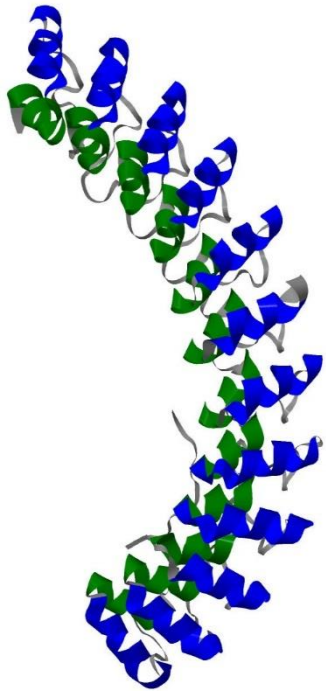
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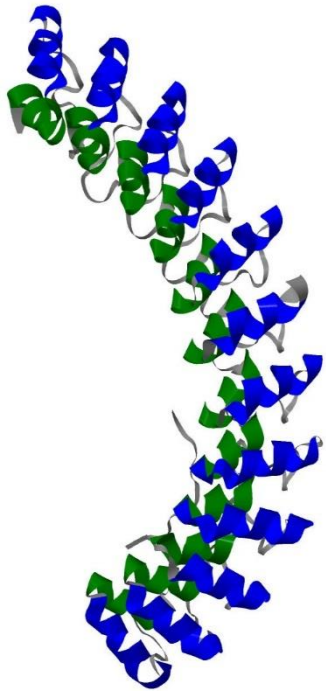
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TRPA1 Structure modeling

TRPA1 ankyrin repeats are phosphorylated
by Cdk5 in the same structural positions

<https://www.ncbi.nlm.nih.gov/pubmed/29352128>

Value of theoretical model

- Close large gap between data on primary structures and data on secondary and tertiary structures of proteins.
- Save time and resources



The SCHOOL OF THEORETICAL MODELING is a new University in Washington DC. The School conducts research in many areas including Biochemistry, Mathematics, Biological Macromolecules, Statistics. List of publications in peer review journals and collaborative projects with other universities and organizations is available on www.schtm.org

The School teaches graduate, undergraduate, semester and summer courses, courses for professional development, and test preparation courses. Our graduate program gives graduate students opportunity to participate in real biomedical research. You are welcome to read publications with participation of graduate students published in Journal of Theoretical Biology and Biochemistry.

To attract new generation of students in the future and advance knowledge, School offers courses for High School and Middle School students interested in Math and Sciences. Parents of college-oriented students find many solutions during our parent-student orientation sessions or introductory test-preparation classes.

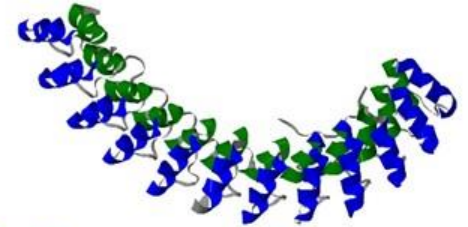
Please send us your questions, explore web site, or schedule an orientation session and come to visit.

YouTube Movie: <http://youtu.be/oBIOL3UXaS0>

LinkedIn Company Page: http://www.linkedin.com/company/the-school-of-theoretical-modeling?trk=top_nav_home

New Topics in Protein Modeling: <http://youtu.be/ZTYHtkvwBIY>

New Topics in Protein Modeling



The School of Theoretical Modeling
teaches course

“Protein Modeling”

for people who work in the field of
structure of biological macromolecules

- Registration information at

www.schtm.org

New topics added to the course this month: helical repeats ankyrin, HEAT/ARM, LRR, PUM, homology, TAL, and other; interactions of helical repeats with multiprotein assemblies (microtubules, inflammasome, virus coat, ...)

Chirality of van der Waals interactions

- Submit amino acid of your protein prior to attending and complete a model during the course



The School of Theoretical Modeling www.schtm.org

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Graduate Program

- Graduate students participate in biomedical research.
 - Read publications with participation of graduate students in Journal of Theoretical Biology, Biochemistry, Glycobiology, and other journals:
 - www.schtm.org/publications
 - Graduate program consists of 4 semester/summer courses and admits students who already have college degree (or at the last year of college).
- Specialties:
 - Biochemistry/Biomedical Research
 - Organic Chemistry/Biomedical Research
 - Biostatistics/Biomedical Research
 - Computer Science/Biomedical Research
 - Science Writing
 - and other
 - Orientation session registration:
 - www.schtm.org

New Topics in Protein Modeling



One day
Course
Semester
Course
Summer
Course
Online
course

Registration:
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Phone:
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The School of Theoretical Modeling teaches course “**Protein Modeling**” for people who work in the field of structure of biological macromolecules.

New topics are constantly added to the course.

Recent new topics and introductory movies (Youtube and LabTube.tv) :

“Structure Alignment of Proteins” <http://youtu.be/TIH0NqqDkPI>

“Helix-helix interfaces: Key positions” <http://youtu.be/SR-SiK23o9Q>
<http://www.labtube.tv/playVideo.aspx?vid=156804>

“Sequence Similarities in 3D” <http://youtu.be/ec5LMLiGVTlc>
<http://www.labtube.tv/playVideo.aspx?vid=160933>

“Prediction of the tertiary structure of Helical Assemblies”
http://lnkd.in/d_qUCf3

“Prediction of the effect of mutations on protein structure”
“Homology Modeling”

Helical Assemblies

Candidate proteins. Structure in progress: Anks1a and Anks1b

Visit Company pages:

Linkedin:

<http://www.linkedin.com/company/the-school-of-theoretical-modeling>

Youtube:

<http://youtu.be/oBIOL3UXaS0> <http://youtu.be/SR-SiK23o9Q>

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