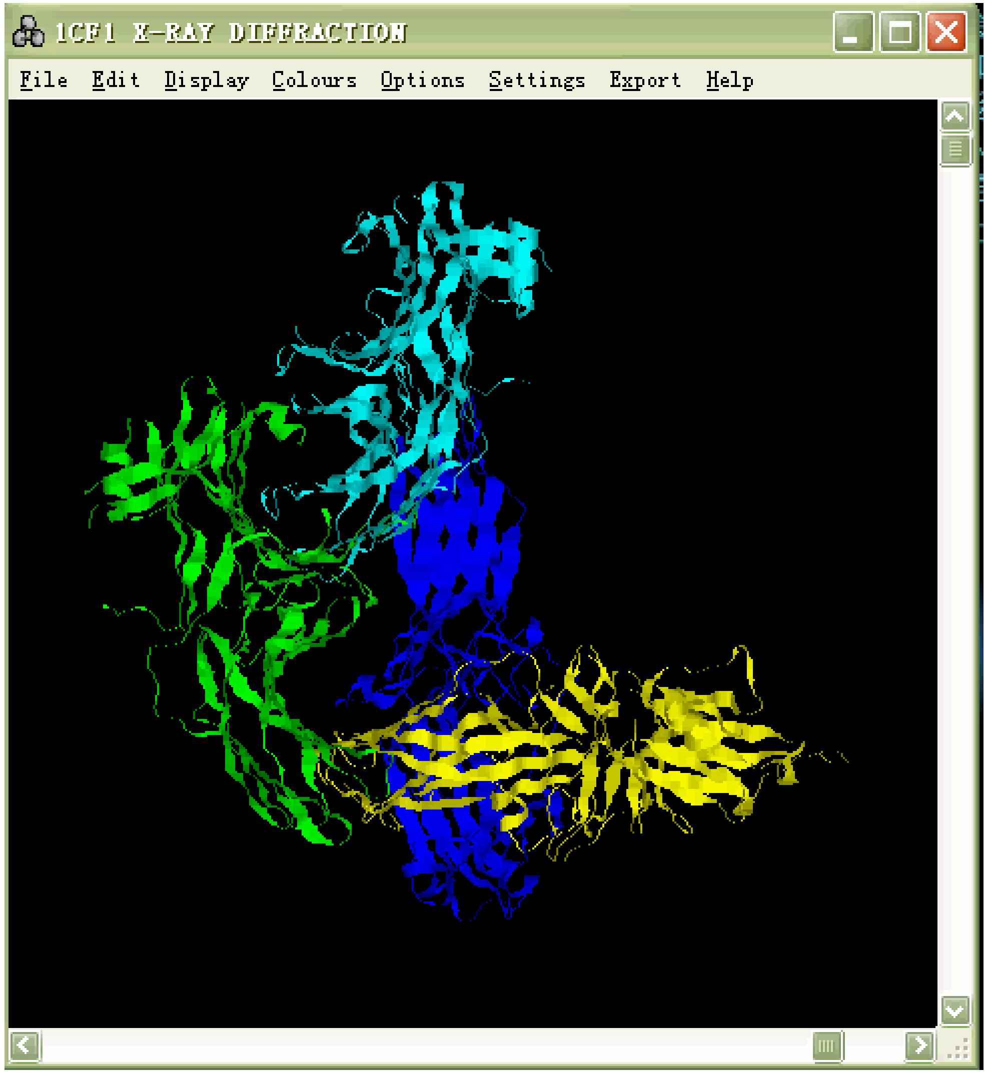
The 2.8 Å crystal structure of visual arrestin : a model for arrestin's regulation

Hirsch JA *etc.*

Cell 97:257-269 (1999)

Presented by Liang

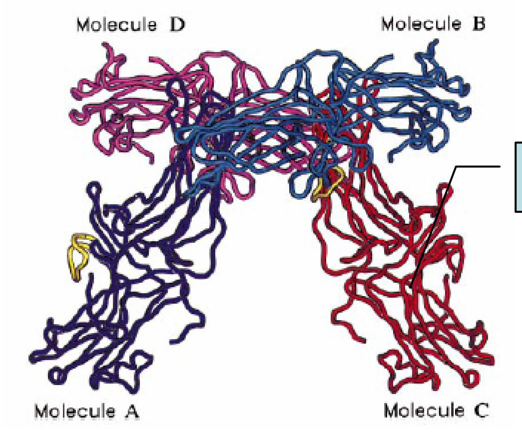


Active state:
monomer;

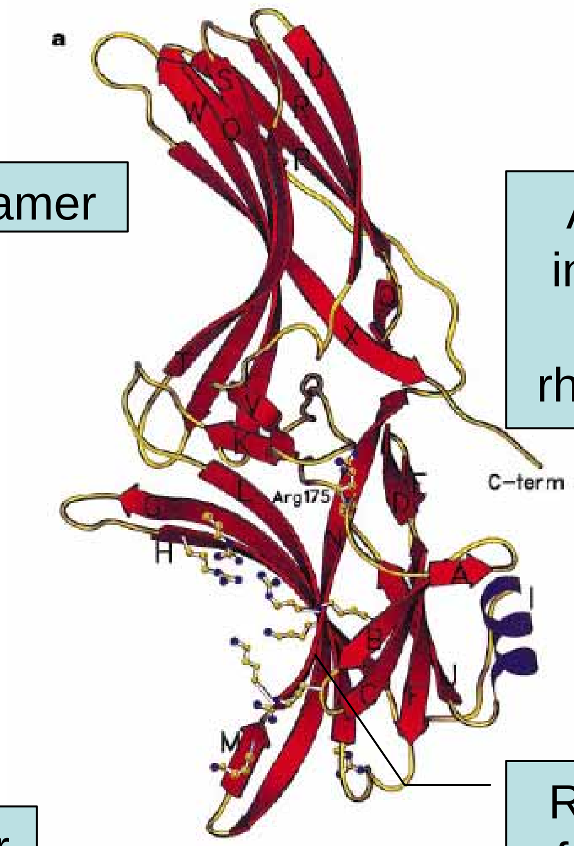
Inactive state:
heterodimer;

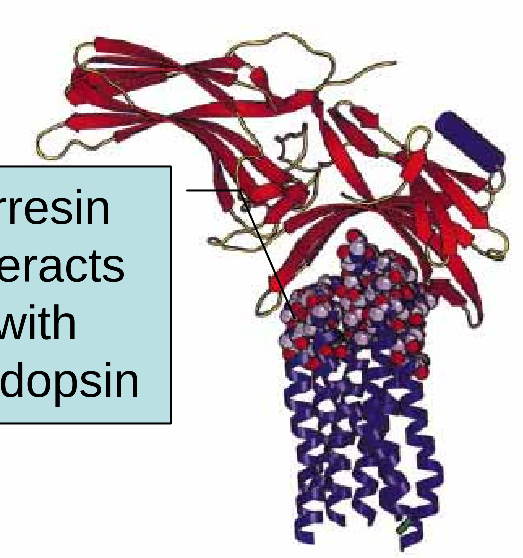
High concentration:
tetramer.

chain A-alpha, BLUE;
chain B-beta, CYAN;
chain C-alpha, GREEN;
chain D-beta, YELLOW.



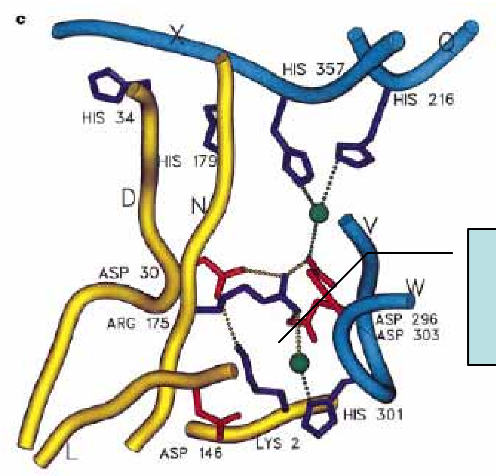
Tetramer





Arresin interacts with rhodopsin

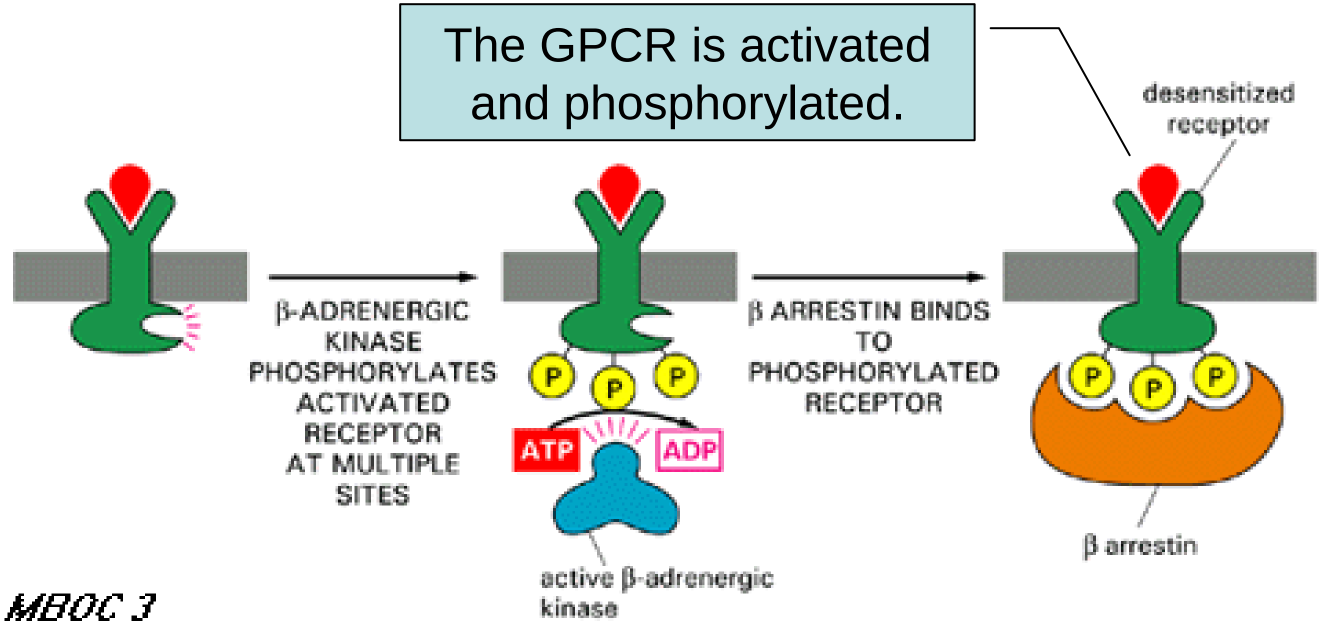
Ribbon diagram of beta-conformer



Polar core

Joachim Granzin *etc*, *Nature*, 1998, **391**:918-921

Arrestin: desensitize GPCR*p

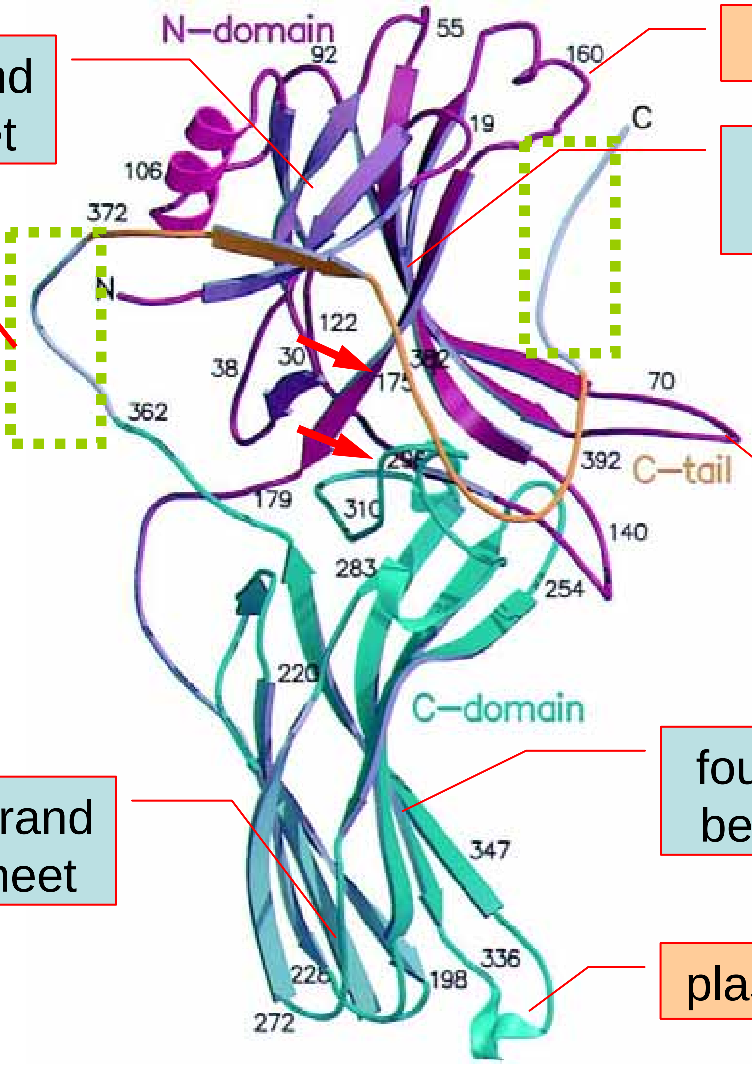


The GPCR is activated and phosphorylated.

MBOC 3

The binding of an arrestin to the phosphorylated receptor prevents the receptor from binding to its G protein and can direct its endocytosis.

Structure of arrestin-alpha



three-strand beta sheet

plastic region ii

four-strand beta sheet

disordered region modeled as polyalanine

plastic region i

four-strand beta sheet

three-strand beta sheet

plastic region iii

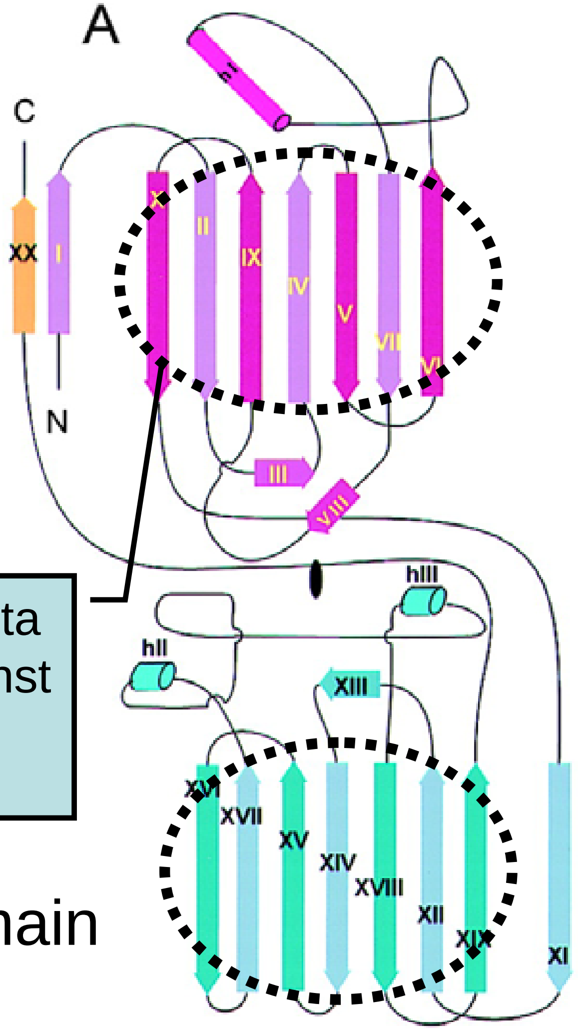
Topology of arrestin

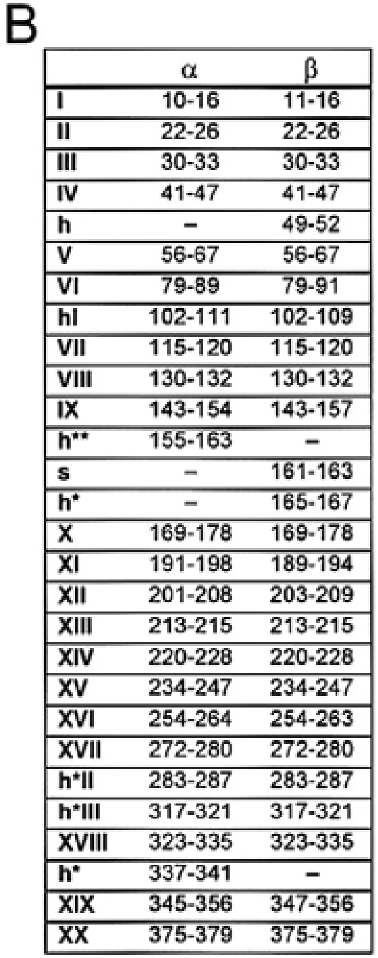
C tail

N domain

C domain

a four-stranded beta sheet packed against a three-stranded beta sheet

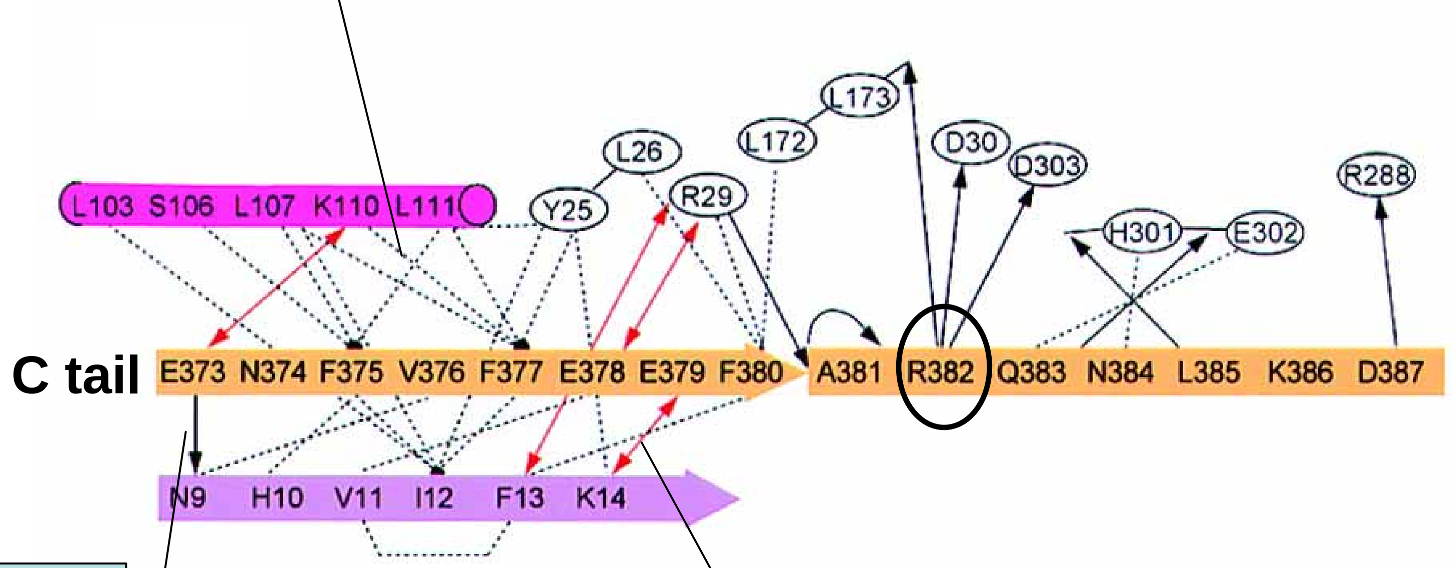




	α	β
I	10-16	11-16
II	22-26	22-26
III	30-33	30-33
IV	41-47	41-47
h	–	49-52
V	56-67	56-67
VI	79-89	79-91
hI	102-111	102-109
VII	115-120	115-120
VIII	130-132	130-132
IX	143-154	143-157
h**	155-163	–
s	–	161-163
h*	–	165-167
X	169-178	169-178
XI	191-198	189-194
XII	201-208	203-209
XIII	213-215	213-215
XIV	220-228	220-228
XV	234-247	234-247
XVI	254-264	254-263
XVII	272-280	272-280
h*II	283-287	283-287
h*III	317-321	317-321
XVIII	323-335	323-335
h*	337-341	–
XIX	345-356	347-356
XX	375-379	375-379

s: strand;
h: alpha-helix;
h*: 3_{10} helix;
h**: helical conformation.

C tail: restrain arrestin inactive

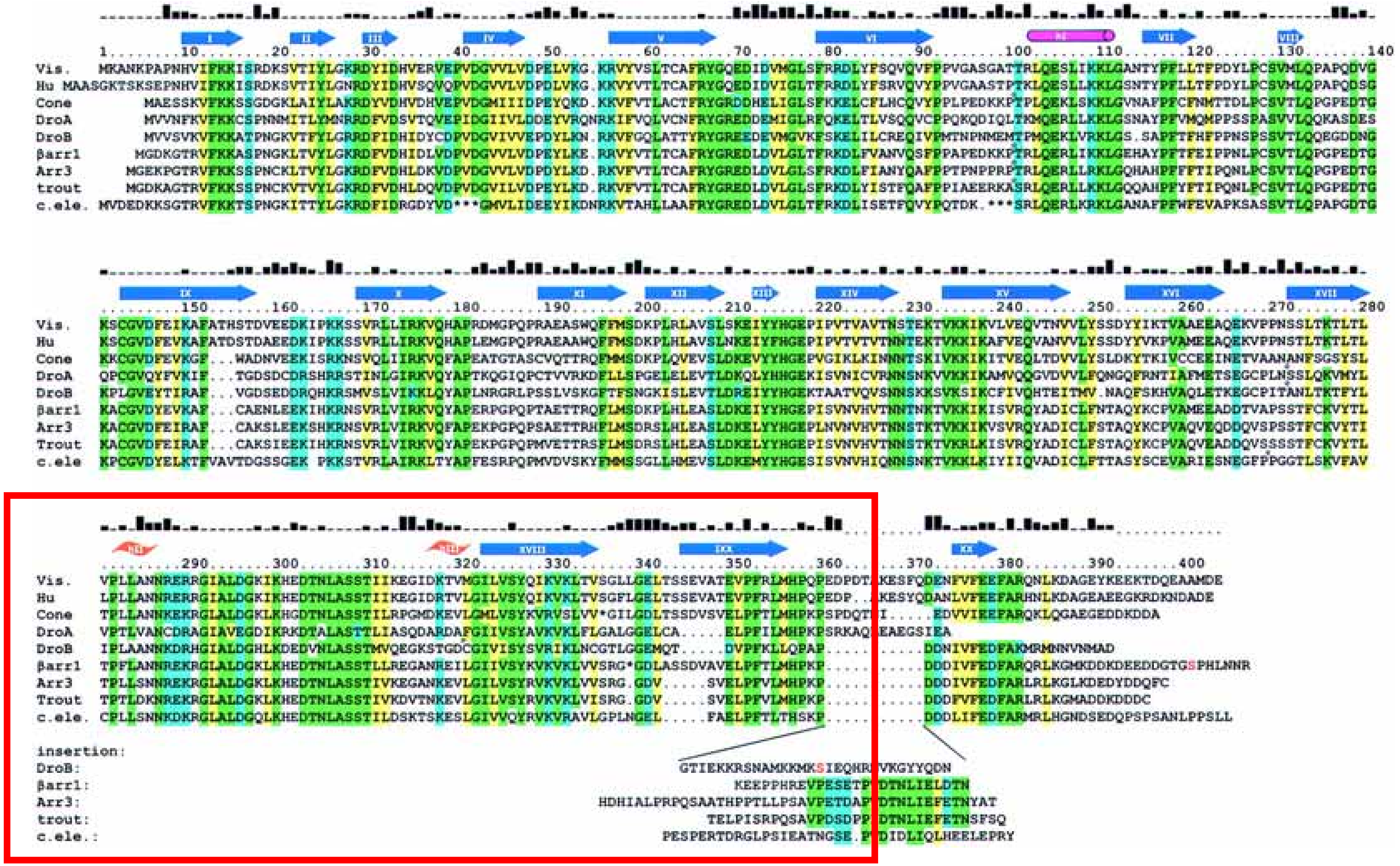


van der Waals contact

hydrogen bond interactions

electrostatic interaction

Critical residues are conserved



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Vis.   MKANKPAPNHVIFKKISRDKSVTIYLGKRDYIDHVERVEPVDGVVLVDPELVKG.KRVYVSLTCAFRYGQEDIDVMGLSFRRDLYFSQVQVFPPVGASGATTRLQESLIKKLGANTYPFLLTFPDYLPCSVMLQPAPQDVG
Hu MAASGKTSKSEPNHVIFKKISRDKSVTIYLGNRDYIDHVSQVQPVDGVVLVDPDLVKG.KKVYVTLTCAFRYGQEDIDVIGLTFRRDLYFSRVQVYPPVGAASTPTKLQESLLKKLGSNTYPFLLTFPDYLPCSVMLQPAPQDSG
Cone        MAESSKVFKKSSGDGKLAIYLAKRDYVDHVDHVEPVDGMIIIDPEYQKD.KKVFVTLACTFRYGRDDHELIGLSFKKELCFLHCQVYPPLPEDKKPTPLQEKLSKKLGVNAFPFCFNMTTDLPCSVTLQPGPEDTG
DroA        MVVNFKVFKKCSPNNMITLYMNRRDFVDSVTQVEPIDGIIVLDDEYVRQNRKIFVQLVCNFRYGREDDEMIGLRFQKELTLVSQQVCPPQKQDIQLTKMQERLLKKLGSNAYPFVMQMPPSSPASVVLQQKASDES
DroB        MVVSVKVFKKATPNGKVTFYLGRRDFIDHIDYCDPVDGVIVVEPDYLKN.RKVFGQLATTYRYGREEDEVMGVKFSKELILCREQIVPMTNPNMEMTPMQEKLVRKLGS.SAPFTFHFPPNSPSSVTLQQEGDDNG
βarr1      MGDKGTRVFKKASPNGKLTVYLGKRDFVDHIDLVDPVDGVVLVDPEYLKE.RRVYVTLTCAFRYGREDLDVLGLTFRKDLFVANVQSFPPAPEDKKPTRLQERLIKKLGEHAYPFTFEIPPNLPCSVTLQPGPEDTG
Arr3      MGEKPGTRVFKKSSPNCKLTVYLGKRDFVDHLDKVDPVDGVVLVDPDYLKD.RKVFVTLTCAFRYGREDLDVLGLSFRKDLFIANYQAFPPTPNPPRPTRLQERLLRKLGQHAHPFFFTIPQNLPCSVTLQPGPEDTG
trout     MGDKAGTRVFKKSSPNCKVTVYLGKRDFVDHLDQVDPVDGVILVDPEYLKD.RKVFVTLTCAFRYGREDLDVLGLSFRKDLYISTFQAFPPIAEERKASRLQERLLKKLGQQAHPFYFTIPQNLPCSVTLQPGPEDTG
c.ele. MVDEDKKSGTRVFKKTSPNGKITTYLGKRDFIDRGDYVD***GMVLIDEEYIKDNRKVTAHLLAAFRYGREDLDVLGLTFRKDLISETFQVYPQTDK.***SRLQERLKRKLGANAFPFWFEVAPKSASSVTLQPAPGDTG

Vis.   KSCGVDFEIKAFATHSTDVEEDKIPKKSSVRLLIRKVQHAPRDMGPQPRAEASWQFFMSDKPLRLAVSLSKEIYYHGEPIPVTVAVTNSTEKTVKKIKVLVEQVTNVVLYSSDYYIKTVAAEEAQEKVPPNSSLTKTLTL
Hu     KSCGVDFEVKAFATDSTDAEEDKIPKKSSVRLLIRKVQHAPLEMGPQPRAEAAWQFFMSDKPLHLAVSLNKEIYFHGEPIPVTVTVTNNTEKTVKKIKAFVEQVANVVLYSSDYYVKPVAMEEAQEKVPPNSTLTKTLTL
Cone   KKCGVDFEVKGF...WADNVEEKISRKNSVQLIIRKVQFAPEATGTASCVQTTRQFMMSDKPLQVEVSLDKEVYYHGEPVGIKLKINNNTSKIVKKIKITVEQLTDVVLYSLDKYTKIVCCEEINETVAANANFSGSYSL
DroA   QPCGVQYFVKIF...TGDSDCDRSHRRSTINLGIRKVQYAPTKQGIQPCTVVRKDFLLSPGELELEVTLDKQLYHHGEKISVNICVRNNSNKVVKKIKAMVQQGVDVVLFQNGQFRNTIAFMETSEGCPLNSSLQKVMYL
DroB   KPLGVEYTIRAF...VGDSEDDRQHKRSMVSLVIKKLQYAPLNRGRLPSSLVSKGFTFSNGKISLEVTLDREIYYHGEKTAATVQVSNNSKKSVKSIKCFIVQHTEITMV.NAQFSKHVAQLETKEGCPITANLTKTFYL
βarr1  KACGVDYEVKAF...CAENLEEKIHKRNSVRLVIRKVQYAPERPGPQPTAETTRQFLMSDKPLHLEASLDKEIYYHGEPISVNVHVTNNTNKTVKKIKISVRQYADICLFNTAQYKCPVAMEEADDTVAPSSTFCKVYTL
Arr3   KACGVDFEIRAF...CAKSLEEKSHKRNSVRLVIRKVQFAPEKPGPQPSAETTRHFLMSDRSLHLEASLDKELYYHGEPLNVNVHVTNNSTKTVKKIKVSVRQYADICLFSTAQYKCPVAQVEQDDQVSPSSTFCKVYTI
Trout  KACGVDFEIRAF...CAKSIEEKIHKRNSVRLVIRKVQYAPEKPGPQPMVETTRSFLMSDRSLHLEASLDKELYYHGEPISVNVHVTNNSTKTVKRLKISVRQYADICLFSTAQYKCPVAQVEADDQVSSSSTFCKVYTL
c.ele  KPCGVDYELKTFVAVTDGSSGEK PKKSTVRLAIRKLTYAPFESRPQPMVDVSKYFMMSSGLLHMEVSLDKEMYYHGESISVNVHIQNNSNKTVKKLKIYIIQVADICLFTTASYSCEVARIESNEGFPPGGTLSKVFAV

Vis.   VPLLANNRERRGIALDGKIKHEDTNLASSTIIKEGIDKTVMGILVSYQIKVKLTVSGLLGELTSSEVATEVPFRLMHPQPEDPDTAKESFQDENFVFEEFARQNLKDAGEYKEEKTDQEAAMDE
Hu     LPLLANNRERRGIALDGKIKHEDTNLASSTIIKEGIDRTVLGILVSYQIKVKLTVSGFLGELTSSEVATEVPFRLMHPQPEDP..AKESYQDANLVFEEFARHNLKDAGEAEEGKRDKNDADE
Cone   TPLLANNKEKRGLALDGKLKHGDTNLASSTILRPGMDKEVLGMLVSYKVRVSLVV*GILGDLTSSDVSVELPFTLMHPKPSPDQTNI.....EDVVIEEFARQKLQGAEGEDDKDDA
DroA   VPTLVANCDRAGIAVEGDIKRKDTALASTTLIASQDARDAFGIIVSYAVKVKLFLGALGGELCA.....ELPFILMHPKPSRKAQ EAEGSIEA
DroB   IPLAANNKDRHGIALDGHLKDEDVNLASSTMVQEGKSTGDCGIVISYSVRIKLNCGTLGGEMQT.....DVPFKLLQPAP..........DDNIVFEDFAKMRMNNVNMAD
βarr1  TPFLANNREKRGLALDGKLKHEDTNLASSTLLREGANREILGIIVSYKVKVKLVVSRG*GDLASSDVAVELPFTLMHPKP..........DDDIVFEDFARQRLKGMKDDKDEEDDGTGSPHLNNR
Arr3   TPLLSNNREKRGLALDGKLKHEDTNLASSTIVKEGANKEVLGILVSYRVKVKLVVSRG.GDV.....SVELPFVLMHPKP..........DDDIVFEDFARLRLKGLKDEDYDDQFC
Trout  TPTLDKNREKRGLALDGKLKHEDTNLASSTIVKDVTNKEVLGILVSYRVKVKLVISRG.GDV.....SVELPFVLMHPKP..........DDDFVFEDFARLRLKGMADDKDDDC
c.ele. CPLLSNNKDKRGLALDGQLKHEDTNLASSTILDSKTSKESLGIVVQYRVKVRAVLGPLNGEL.....FAELPFTLTHSKP..........DDDLIFEDFARMRLHGNDSEDQPSPSANLPPSLL

insertion:
DroB:                            GTIEKKRSNAMKKMKSIEQHR VKGYYQDN
βarr1:                                 KEEPPHREVPESETP DTNLIELDTN
Arr3:              HDHIALPRPQSAATHPPTLLPSAVPETDAP DTNLIEFETNYAT
trout:                              TELPISRPQSAVPDSDPP DTNLIEFETNSFSQ
c.ele.:                       PESPERTDRGLPSIEATNGSE.P DIDLIQLHEELEPRY
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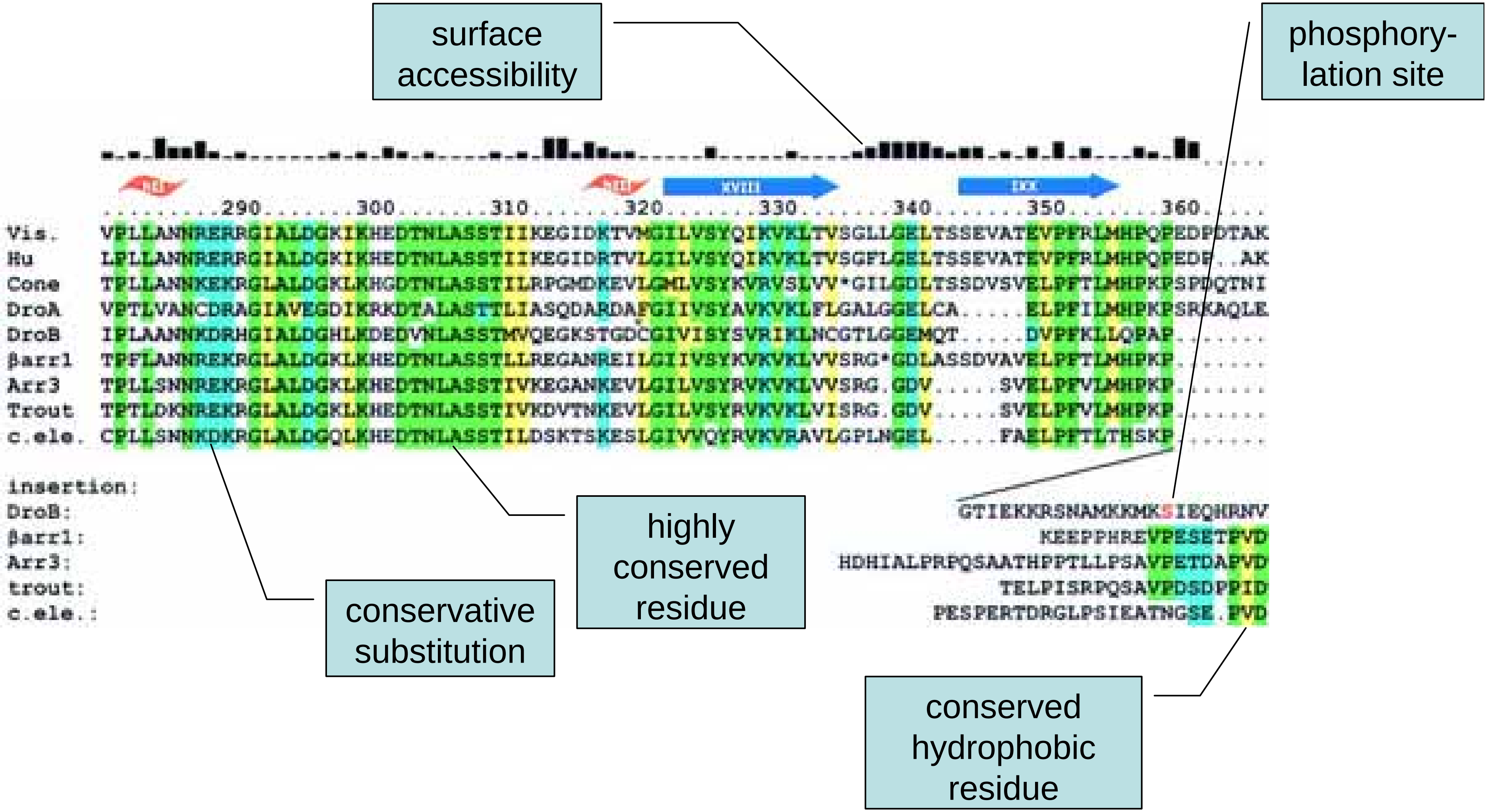

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          .........290.......300.......310.......320.......330.......340.......350.......360.....
Vis.      VPLLANNRERRGIALDGKIKHEDTNLASSTIIKEGIDKTVMGILVSYQIKVKLTVSGLLGELTSSEVATEVPFRLMHPQPEDPDTAK
Hu        LPLLANNRERRGIALDGKIKHEDTNLASSTIIKEGIDRTVLGILVSYQIKVKLTVSGFLGELTSSEVATEVPFRLMHPQPEDP..AK
Cone      TPLLANNKEKRGLALDGKLKHGDTNLASSTILRPGMDKEVLGMLVSYKVRVSLVV*GILGDLTSSDVSVELPFTLMHPKPSPDQTNI
DroA      VPTLVANCDRAGIAVEGDIKRKDTALASTTLIASQDARDAFGIIVSYAVKVKLFLGALGGELCA.....ELPFILMHPKPSRKAQLE
DroB      IPLAANNKDRHGIALDGHLKDEDVNLASSTMVQEGKSTGDCGIVISYSVRIKLNCGTLGGEMQT.....DVPFKLLQPAP......
βarr1     TPFLANNREKRGLALDGKLKHEDTNLASSTLLREGANREIILGIIVSYKVKVKLVVSRG*GDLASSDVAVELPFTLMHPKP......
Arr3      TPLLSNNREKRGLALDGKLKHEDTNLASSTIVKEGANKEVLGILVSYRVKVKLVVSRG.GDV.....SVELPFVLMHPKP......
Trout     TPTLDKNREKRGLALDGKLKHEDTNLASSTIVKDVTNKEVLGILVSYRVKVKLVISRG.GDV.....SVELPFVLMHPKP......
c.ele.    CPLLSNNKDKRGLALDGQLKHEDTNLASSTILDSKTSKESLGIVVQYRVKVRAVLGPLNGEL.....FAELPFTLTHSKP......

insertion:
DroB:                                 GTIEKKRSNAMKKMKSIEQHRNV
βarr1:                                       KEEPPHREVPESETPVD
Arr3:                    HDHIALPRPQSAATHPPTLLPSAVPETDAPVD
trout:                                     TELPISRPQSAVPDSDPPID
c.ele.:                           PESPERTDRGLPSIEATNGSE.PVD
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surface accessibility

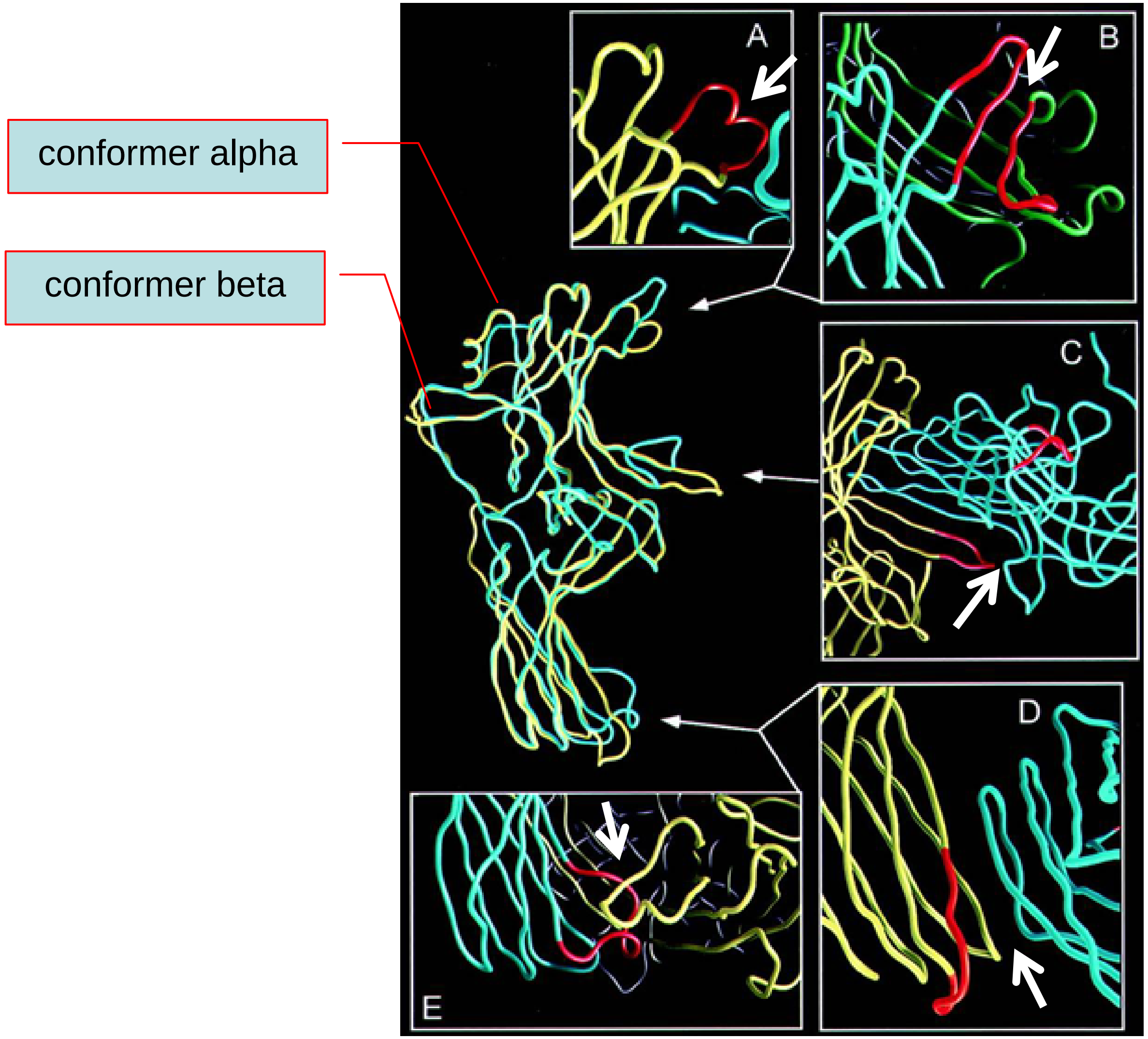
phosphorylation site

highly conserved residue

conservative substitution

conserved hydrophobic residue

Plasticity of Arrestin



A, helical conformation of residues 155-165;

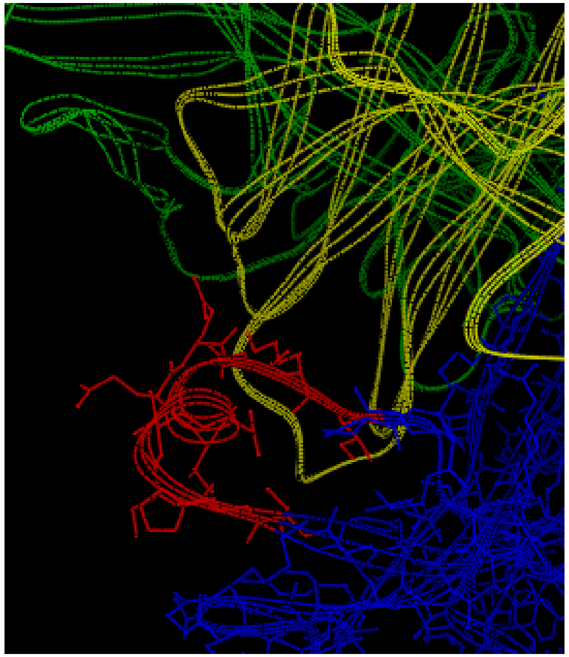
B, strand-turn-strand conformation;

C, dimer interface between alpha and beta (residues 68-79);

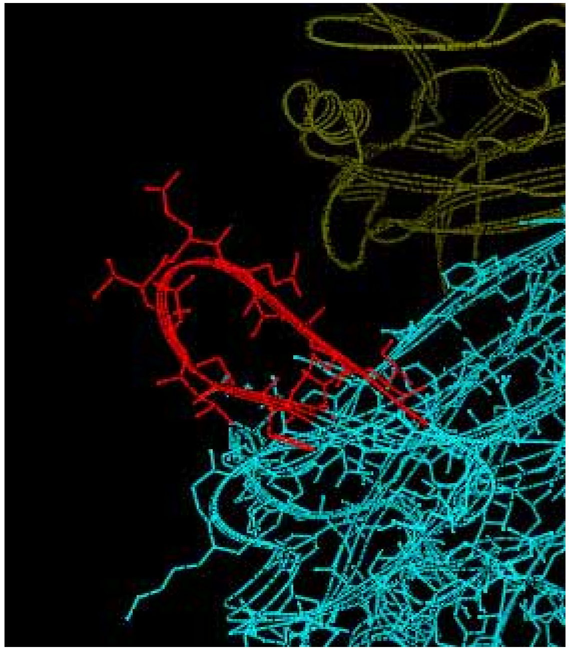
D, interface between alpha and beta (residues 337-347);

E, dimer interface between alpha and beta.

A.
residues 155-165



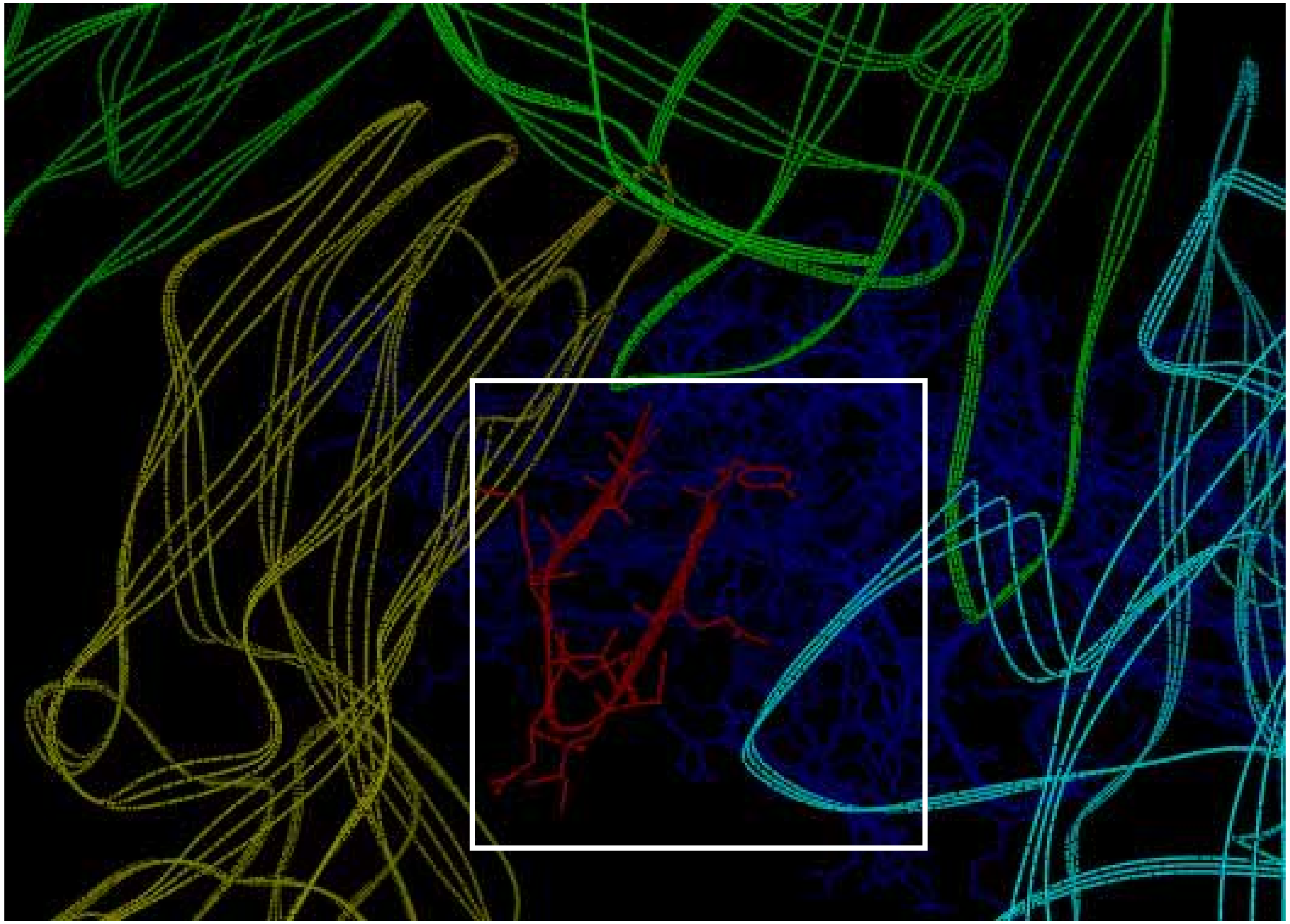
arresin-alpha:
helix



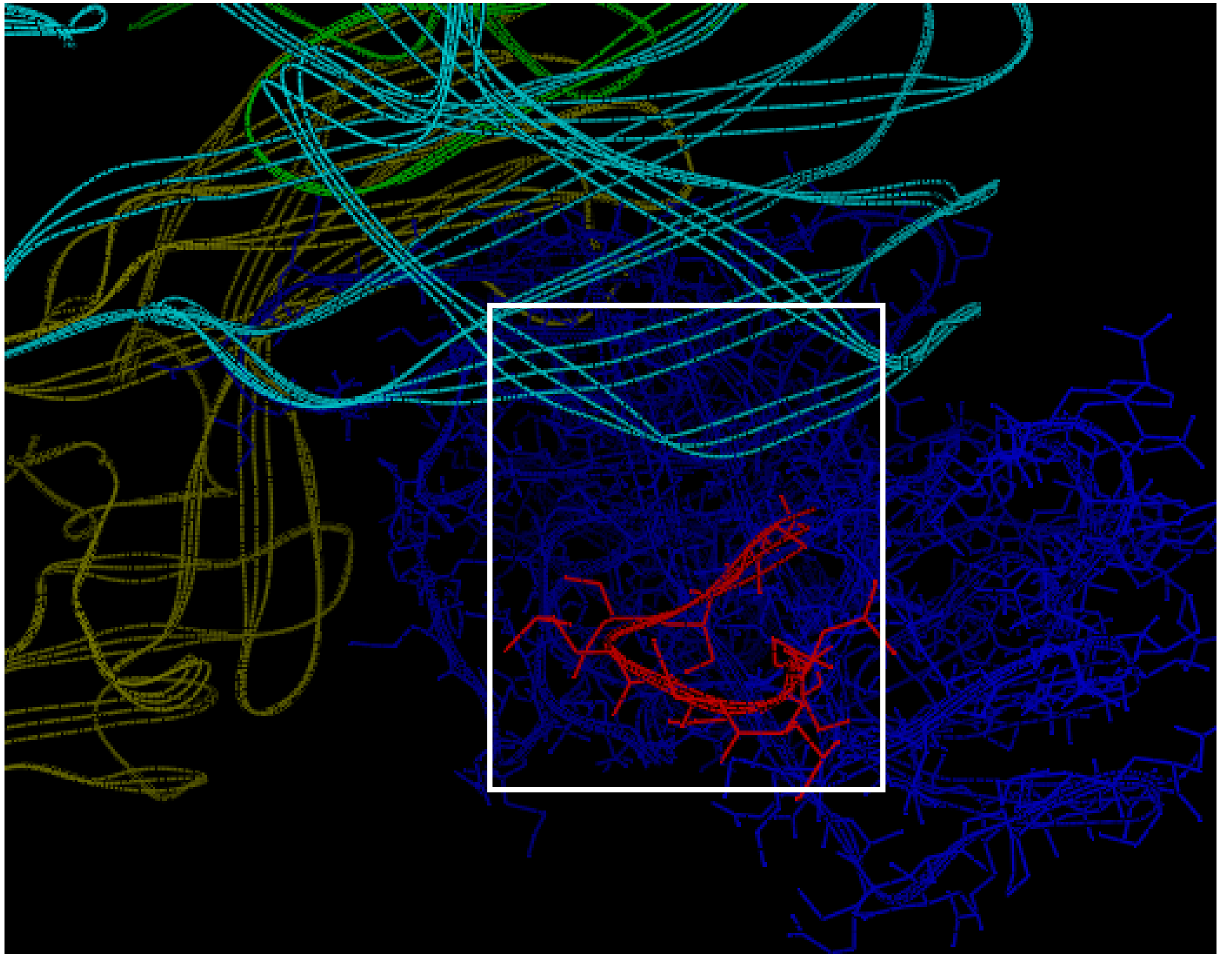
arresin-beta:
strand-turn-strand

C.

interface between alpha and beta

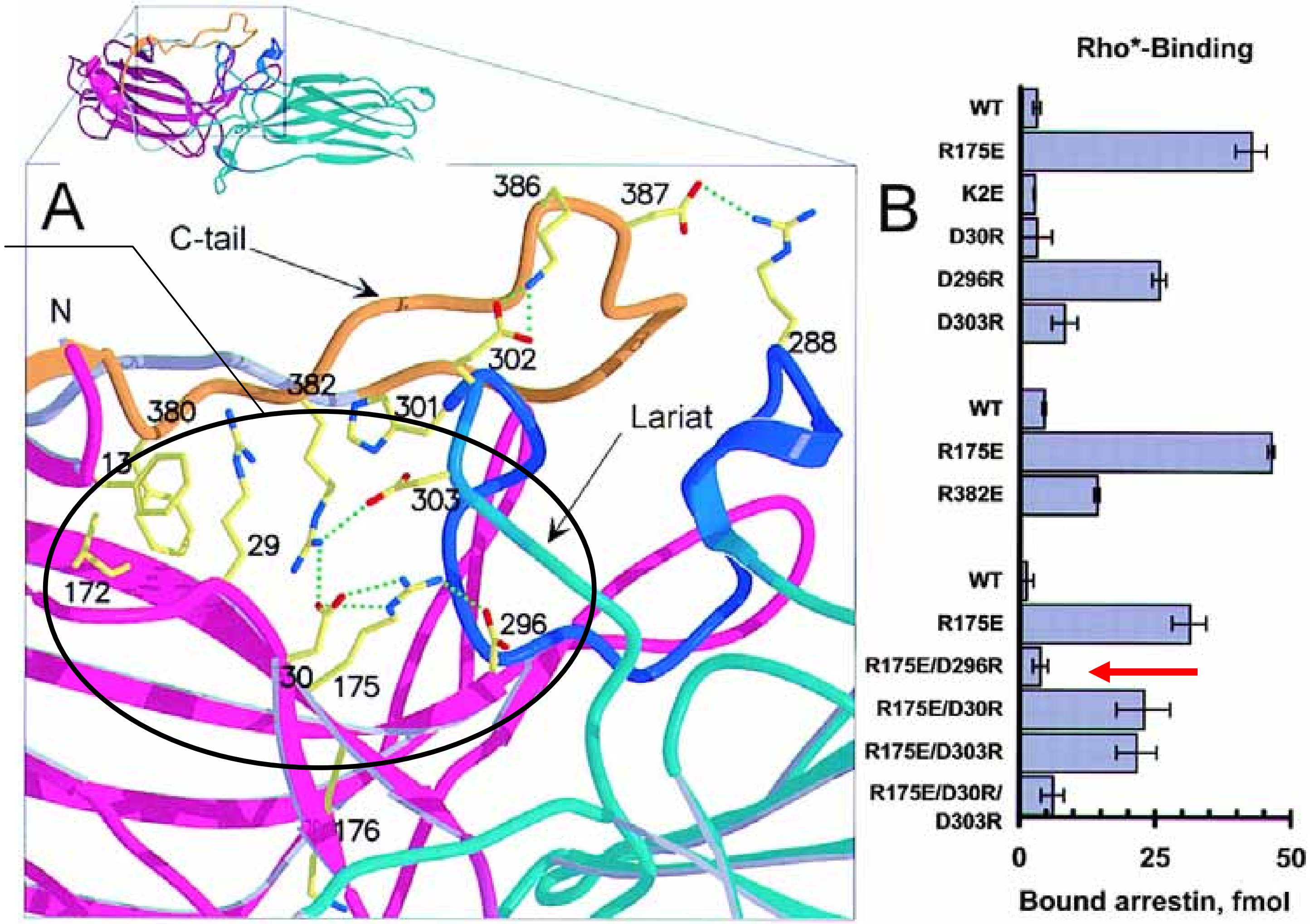


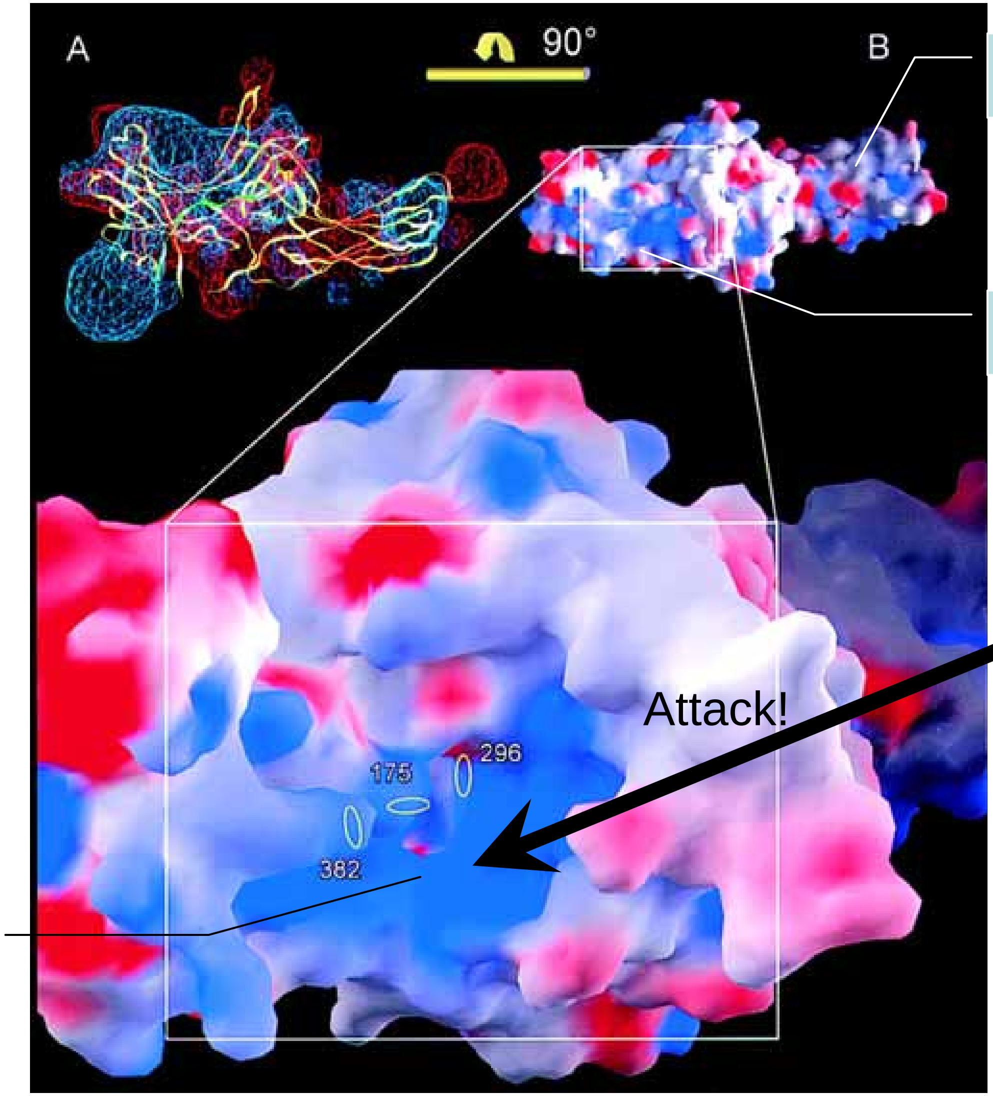
D.
interface between alpha and beta



Polar core: energetic un-favor

C tail
covers
polar core





C domain

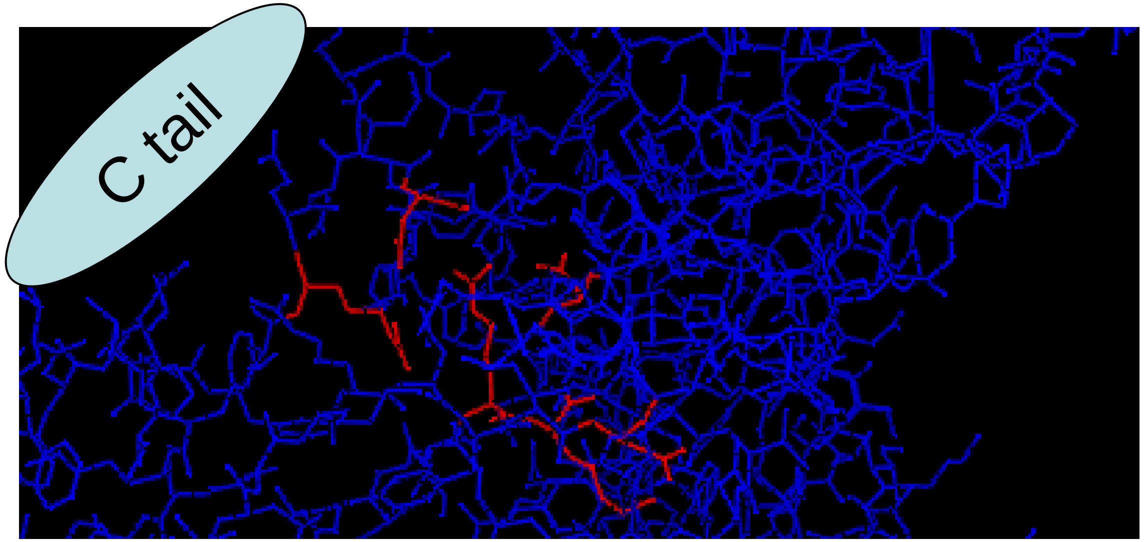
N domain

P-

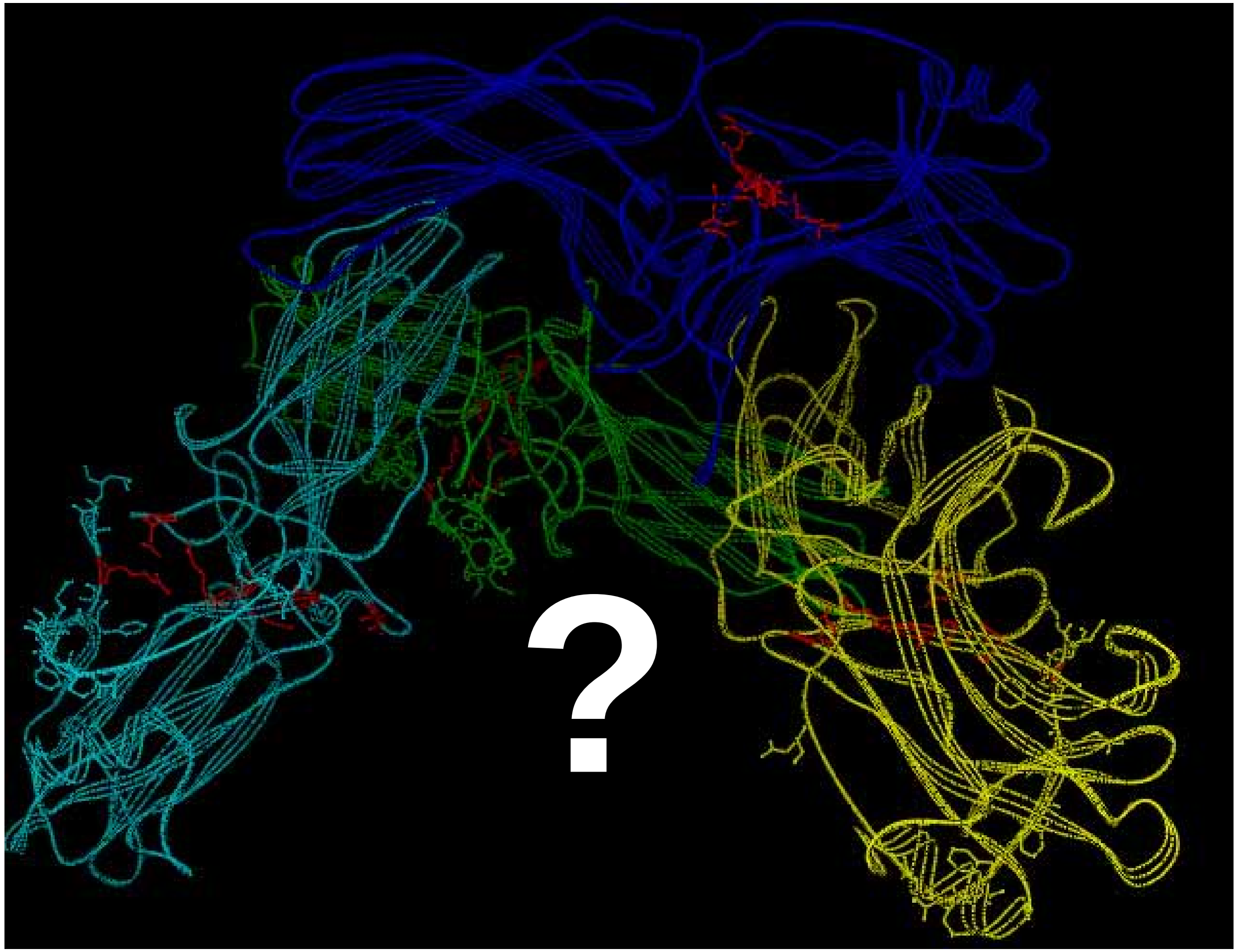
Attack!

positive charge

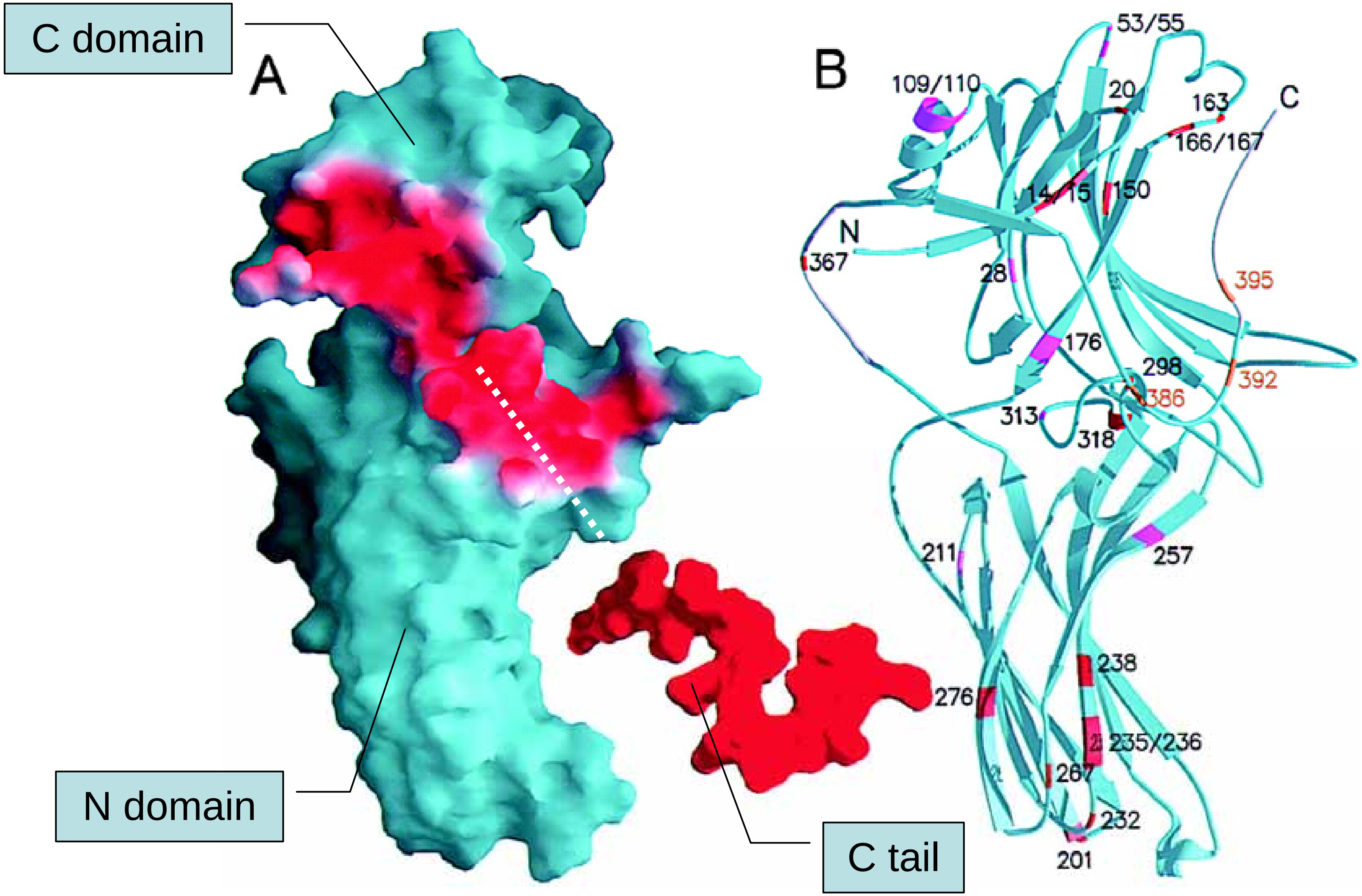
Electrostatic Potential of arrestin



- charged side chains are buried;
- forming charge-charge interaction to keep neutrality;



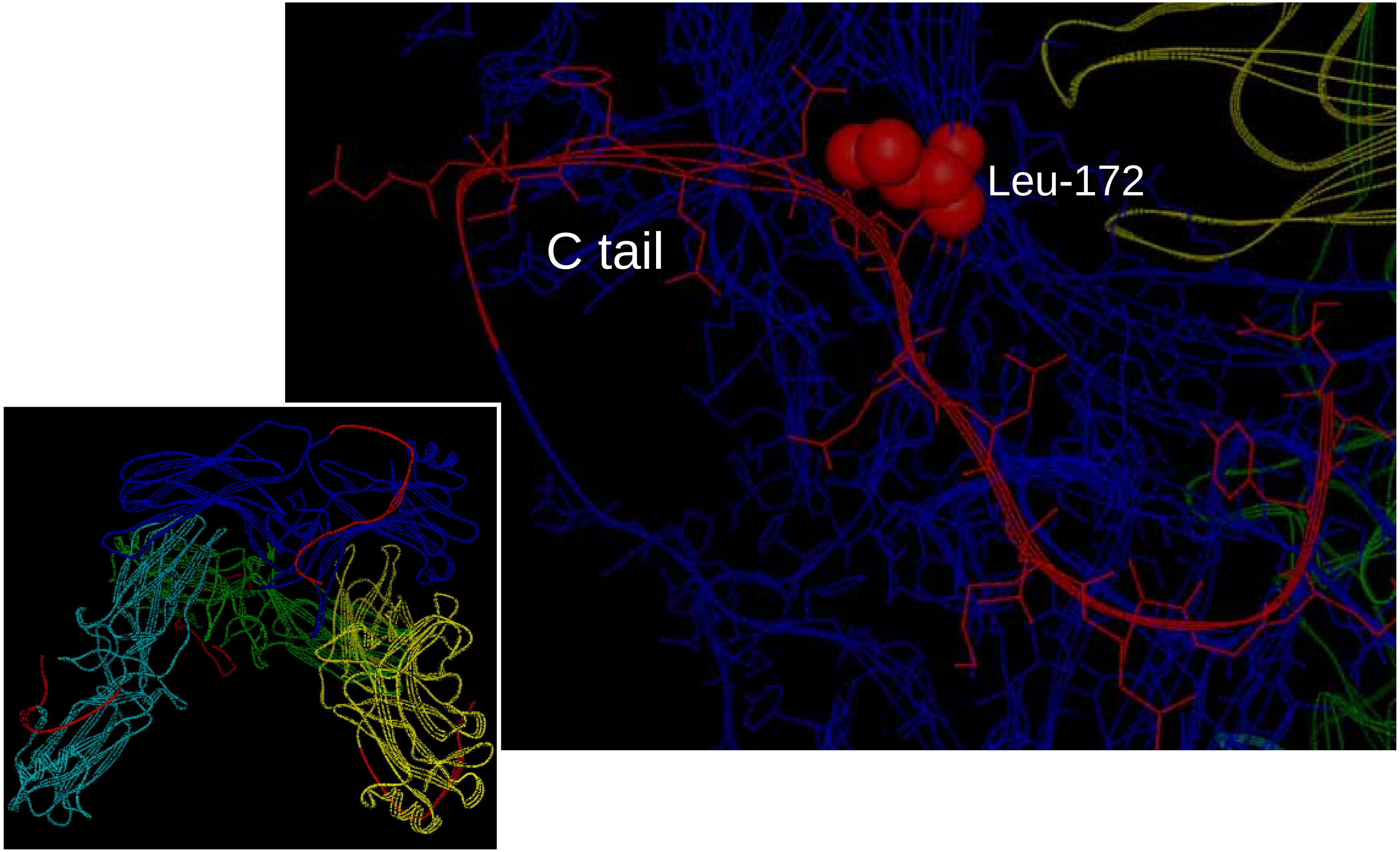
Cleavage C tail actives arrestin



C domain

N domain

C tail


Leu-172
C tail

Model for arrestin's activation

- C tail & balanced polar core maintains basal state of arrestin
- Rho*p destabilize polar core
- Arrestin rearranges into active state
- Form arrestin-receptor complex

Q & A

Thanks.

Oct. 21, 2003