

Fundamentals of Protein Chemistry
Prof. Swagata Dasgupta
Department of Chemistry
Indian Institute of Technology, Kharagpur

Module - 11
Protein Macromolecule Interactions II
Lecture - 53
Protein Peptide Interactions

In our 2nd module on protein macromolecular interactions we have discussed protein-protein interactions, looked at the specific domains that are involved, the types of interfaces that are involved in these very important complex formations that occur. In this lecture we will look at protein peptide interactions with specific examples.

(Refer Slide Time: 00:39)

CONCEPTS COVERED

- Importance of protein-peptide interactions
- Specifics of protein – peptide interactions
- Peptides as therapeutics
- Mechanism of cellular uptake

The slide features a video inset of Prof. Swagata Dasgupta in the bottom right corner. At the bottom, there are logos for IIT Kharagpur and NPTEL.

The concepts covered will be the importance of these protein peptide interactions, the specifics, peptides as therapeutics and how they can be used for therapeutics in terms of their cellular uptake.

(Refer Slide Time: 00:53)

KEYWORDS

- Peptide therapeutics
- Angiotensin-converting enzyme (ACE)
- Cell-penetrating peptides (CPPs)
- Peptidomimetic compounds

These [refer to slide] are the specific keywords that we will be looking into.

(Refer Slide Time: 00:58)

Protein-peptide interactions

There are various ways through which proteins can interact with short peptide sequences.

Interactions can be:

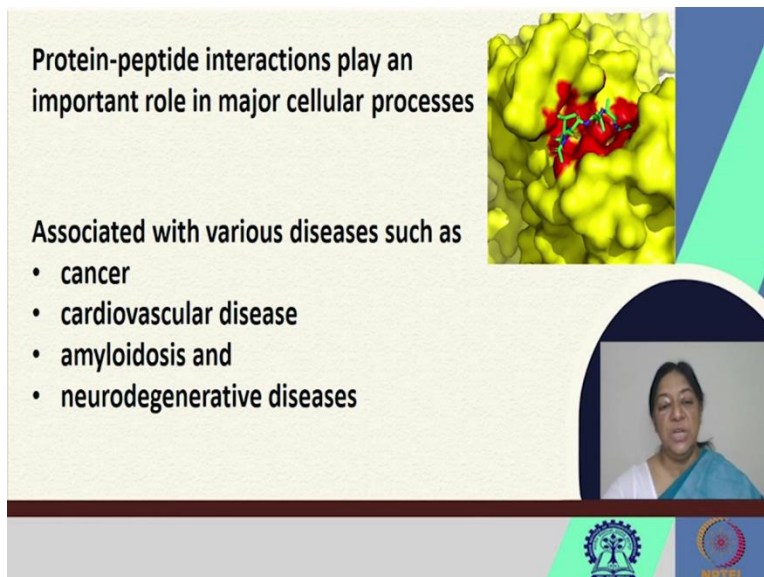
- sequence dependent or
- sequence independent

Protein-protein interactions (PPIs) play a key role in the biological as well as pathogenic processes in cells

When we look at protein peptide interactions there are of course, a subset of protein-protein interactions. They play a key role in the biological as well as pathogenic processes in cells. So, there are various ways in which these proteins can interact with the short peptide sequences. Their interactions can be sequence dependent or sequence independent. Depending upon the type

of protein or the type of interaction that is involved, we will discuss this in terms of the type of interface that is present.

(Refer Slide Time: 01:38)



Protein-peptide interactions play an important role in major cellular processes

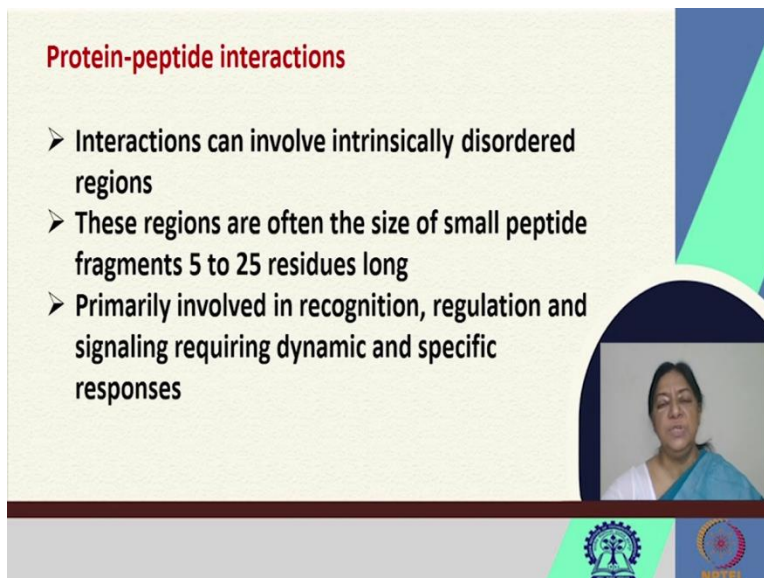
Associated with various diseases such as

- cancer
- cardiovascular disease
- amyloidosis and
- neurodegenerative diseases

The slide features a 3D molecular model of a protein-peptide interaction, a video inset of the presenter, and logos for IIT Bombay and NPTEL.

We know that protein peptide interactions will play an important role in major cellular processes, as a result they are associated with various diseases as well; such as cancer, cardiovascular diseases, amyloidosis and neurodegenerative disorders.

(Refer Slide Time: 01:58)



Protein-peptide interactions

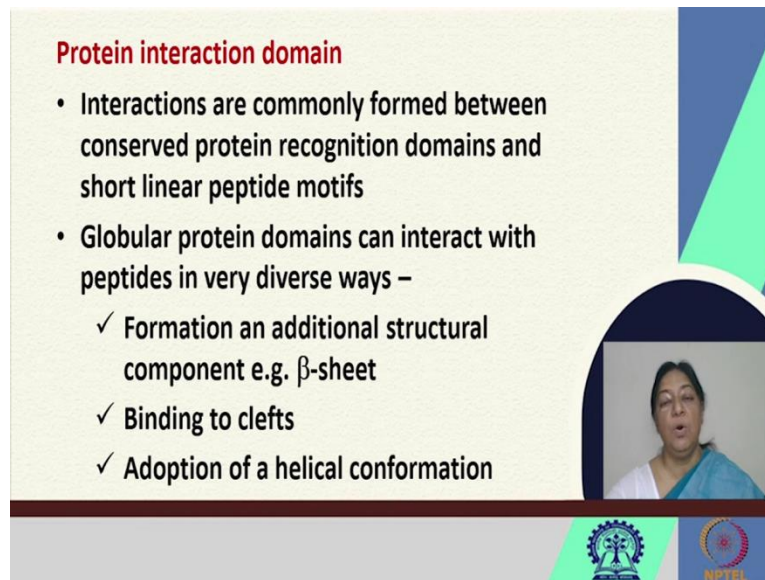
- Interactions can involve intrinsically disordered regions
- These regions are often the size of small peptide fragments 5 to 25 residues long
- Primarily involved in recognition, regulation and signaling requiring dynamic and specific responses

The slide features a video inset of the presenter and logos for IIT Bombay and NPTEL.

The protein peptide interactions in general involve intrinsically disordered regions in proteins, which we will be discussing in our lecture on intrinsically disordered proteins. The regions are often the size of small peptide fragments, usually ranging from a 5 to 25 residue long fragment

and they are involved in recognition, regulation and the signaling that requires dynamic and specific responses. So the specificity and the affinity are both very important in these processes that involved protein protein, protein peptide interactions.

(Refer Slide Time: 02:42)



Protein interaction domain

- Interactions are commonly formed between conserved protein recognition domains and short linear peptide motifs
- Globular protein domains can interact with peptides in very diverse ways –
 - ✓ Formation an additional structural component e.g. β -sheet
 - ✓ Binding to clefts
 - ✓ Adoption of a helical conformation

The slide features a light green background with a dark blue and light green geometric design on the right side. A small video inset in the bottom right corner shows a woman speaking. At the bottom of the slide, there are two logos: the Indian Institute of Technology (IIT) logo on the left and the NPTEL logo on the right.

The protein interaction domain. These interactions are commonly formed between conserved protein recognition domains and short linear peptide motifs. The globular protein domains can interact with peptides in very diverse ways, where they can have a structure that adapts to the specific interaction that is going to occur.

For example, there may be the formation of an additional structural component or the specific binding to clefts or the adoption of a helical conformation, that is going to allow this specific interaction to occur in a manner where the protein will adopt to the specific peptide or the protein that it is interacting with.

(Refer Slide Time: 03:38)

Protein-peptide interactions

Protein recognition of peptides
Geometric and chemical complementarity

Protein interaction domains

Peptide fragments can interact with protein binding domains

Binding of a high affinity phosphotyrosyl peptide to the Src SH2 domain

PDB ID: 1SP5

The slide features a 3D surface model of a protein domain in purple. A red ribbon structure representing a peptide is bound within a specific cleft of the protein. A blue oval highlights the binding site. To the right, there is a small inset video of a woman speaking. The slide includes logos for a university and NPTEL at the bottom.

In the protein-protein peptide interactions, we therefore have the protein recognition of these peptides and as we looked at previously in the terms of the protein-protein recognition interactions, they involve a geometric and a chemical complementarity. So, the protein interaction domains as we see [refer to slide] in this specific picture here, can have the peptide fragments that interact with the protein binding domains.

Here we have the binding of a high affinity phosphotyrosyl peptide to the Src SH2 domain, something that we discussed in a previous lecture. So the distinction or the cavity or the cleft that holds this peptide in the specific protein domain, is required for the specific interaction to occur, for the function of the protein to progress.

(Refer Slide Time: 04:34)

Protein interaction domains

PDB ID: 3OV1

SH2 domain in complex with a pYXN derived tripeptide

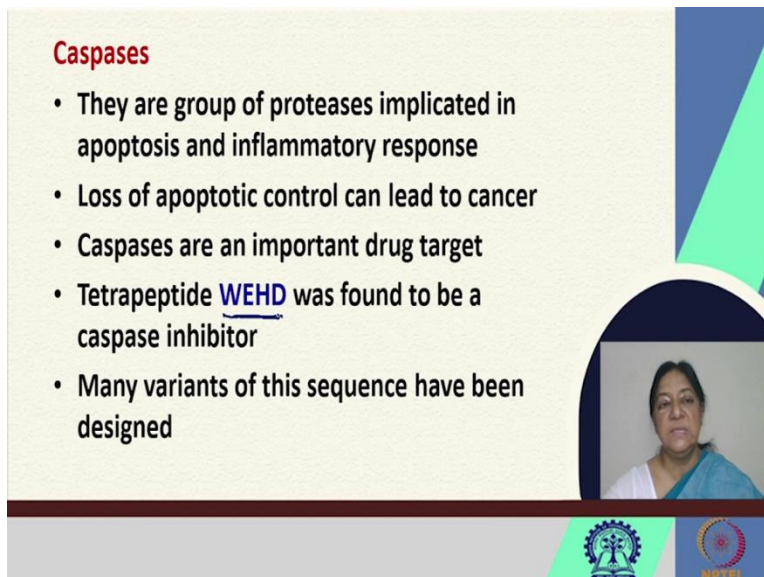
PDB ID: 1N5Z

SH3 domain in complex with a polyproline peptide

The slide displays two 3D surface models of protein domains. The left model is green and labeled 'SH2 domain in complex with a pYXN derived tripeptide' with PDB ID: 3OV1. The right model is dark grey and labeled 'SH3 domain in complex with a polyproline peptide' with PDB ID: 1N5Z. Both models show a red peptide chain bound to the protein surface. A small inset video of a woman speaking is located in the bottom right corner. The slide includes logos for a university and NPTEL at the bottom.

When we look at these two different types of proteins the SH3 and the SH2, the SH3 domain is shown [refer to slide] here in complex with a polyproline peptide and the SH2 domain in complex with a phosphotyrosyl derived tripeptide. So the interactions as we can see, are very specific in the way they interact with the domain that is present on the protein.

(Refer Slide Time: 05:05)



Caspases

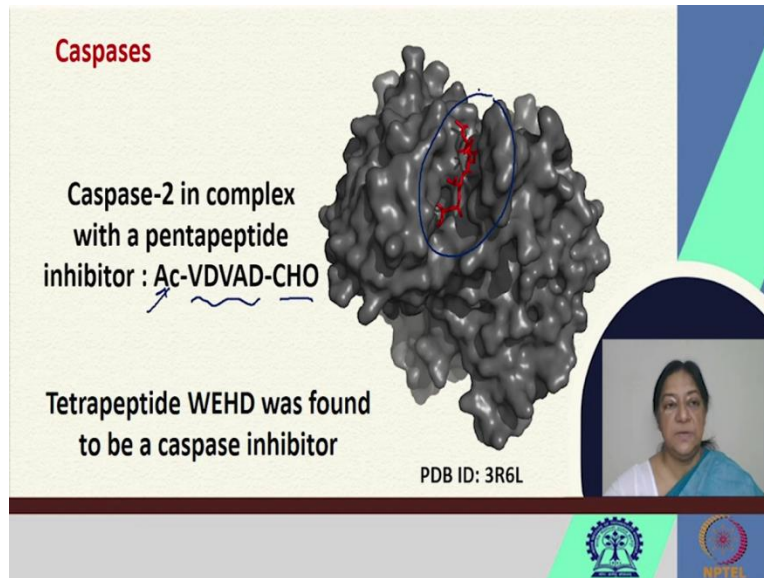
- They are group of proteases implicated in apoptosis and inflammatory response
- Loss of apoptotic control can lead to cancer
- Caspases are an important drug target
- Tetrapeptide WEHD was found to be a caspase inhibitor
- Many variants of this sequence have been designed

The slide features a light green background with a blue and green geometric design on the right side. A small video inset in the bottom right corner shows a woman with dark hair wearing a blue and white sari. At the bottom of the slide, there are two logos: a circular emblem on the left and a logo with the text 'WPI' on the right.

We will look at some specific examples and later on see how specific peptides can be developed and designed, to prevent or to inhibit the action of specific enzymes or specific proteins in their protein-protein complex formation. The caspases are one such example that we will be looking at. These are a group of proteases that are implicated in apoptosis, that is programmed cell death and inflammatory responses.

The loss of this apoptotic control can lead to cancer. Thus, these caspases are an important drug target. The tetrapeptide WEHD, has been found to be a caspase inhibitor. This means that any development based on the design of this tetrapeptide, a knowledge of where it binds on caspase, is going to be useful for the design of specific peptides that would inhibit the action of this protein. Many variants of the sequence have been designed and developed for or to act as a caspase inhibitor.

(Refer Slide Time: 06:19)



So with the knowledge that the tetrapeptide acted as a caspase inhibitor, there were several other peptides that were developed where caspase-2 is shown in complex with the pentapeptide that has an acetyl N terminus, followed by an aldehyde at the end; where we have this specific pentapeptide sequence, that occupies the pocket in a sense that it is going to act as a caspase inhibitor.

(Refer Slide Time: 06:50)



Estrogen receptors

They are receptors that are activated by the estrogen hormone, important for -

- Central nervous system function
- Regulation of reproduction
- Maintenance of bone density

Breast and endometrial cancers are fueled when the hormone estrogen attaches to these receptors

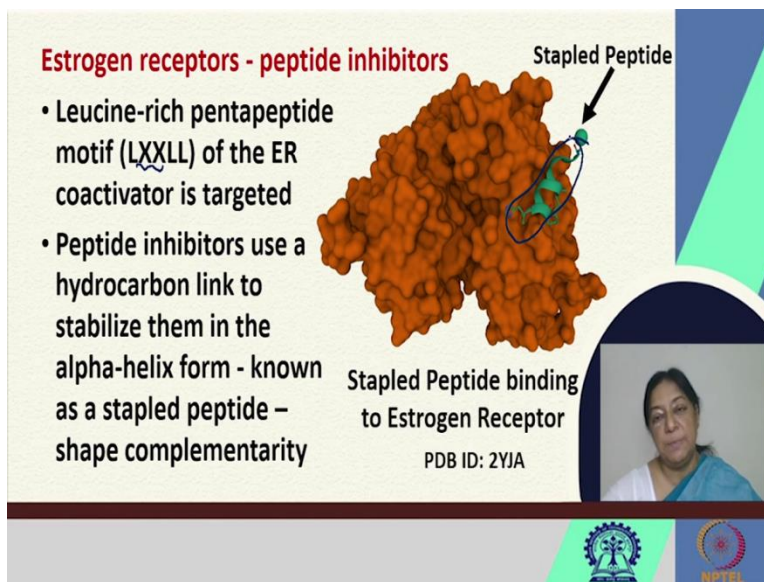
Can be a drug target



We look at the example of estrogen receptors. Estrogen receptors are receptors that are activated by the estrogen hormone. These are important for central nervous system functions, for regulation of reproduction and for the maintenance of bone density.

This means that breast and endometrial cancers are fueled when the hormone estrogen attaches to these receptors. So, they can be used as a drug target to develop inhibitors, based on the structure of the domain that is interacting with the peptide.

(Refer Slide Time: 07:30)



Looking at estrogen receptor peptide inhibitors, there is a leucine rich pentapeptide motif that is LXXLL; XX indicating that there could be different amino acids present at this location. So this leucine rich pentapeptide motif of the estrogen receptor co-activator is targeted.

The peptide inhibitors in this case, use a hydrocarbon link to stabilize themselves in the alpha helix form and this is called a stapled peptide. So we are careful about the geometric complementarity or the shape complementarity, that keeps this intact in a way that it is going to be able to interact with the specific domain on the estrogen receptor, thus preventing the action of the estrogen receptor in a manner that would be desired to prevent any complications from a disease point of view.

So when we look [refer to slide] at this stapled peptide, we look at the stapled peptide binding to the estrogen receptor in this particular structure.

(Refer Slide Time: 08:47)

Bcl-2 (B-cell lymphoma 2)

Regulator protein that regulates cell death (apoptosis)

Bcl-2 has been the target of drug design strategies

Structural groove interacts with binding partners

Peptide based drug design against Bcl-2 has been developed as an approach

Complex of Bcl-2 with a 25-residue peptide from a pro-apoptotic protein

PDB ID: 1G5J

The slide features a 3D molecular model of the Bcl-2 protein, represented as a green surface with a blue ribbon structure. A 25-residue peptide is shown as an orange ribbon, bound within a specific structural groove of the protein. The text on the left lists key facts about Bcl-2 and its role as a drug target. The text on the right describes the complex shown in the model. The PDB ID 1G5J is noted below the model. A small inset video in the bottom right corner shows a woman in a blue sari speaking. Logos for IIT Bombay and NPTEL are visible at the bottom right of the slide.

In the Bcl-2, the B-cell lymphoma 2, this is a regulator protein that regulates cell death that is apoptosis. This has been the target also of drug design strategies. In this case there is a structural groove that interacts with the binding partners. So taking cue from the type of binding partners that could be involved in interaction with the groove, there are peptide based drug design approaches to this Bcl-2 that has been developed.

So this [refer to slide] is the structure of Bcl-2 that is in complex with the 25 residue peptide from another pro-apoptotic protein. What we see is, we see this 25 residue peptide adopting a conformation that is going to make it fit into the structural groove, that acts as a binding partner in this case.

(Refer Slide Time: 09:51)

Protein – protein interface for drug design

Different subunits of proteins often forms complexes to get into their functional forms

Subunits or monomers

Functional protein

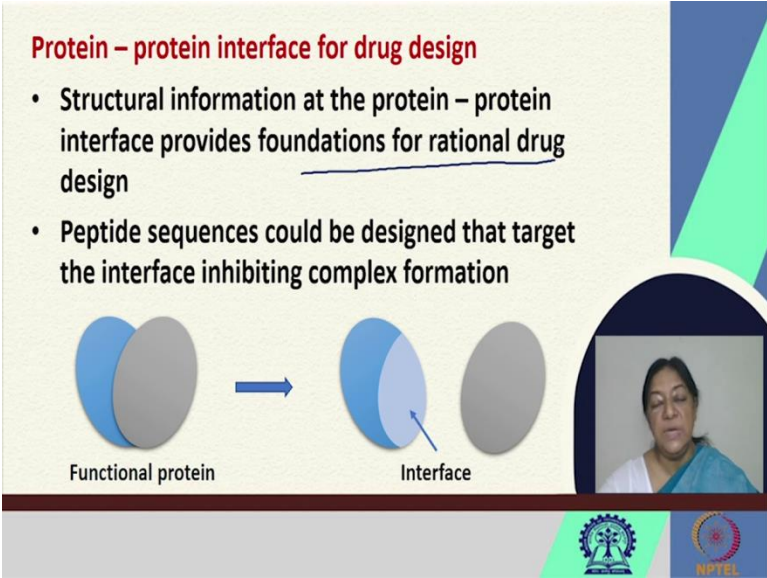
The diagram illustrates the process of protein complex formation. On the left, two separate subunits are shown: a blue oval and a grey oval. An arrow points to the right, where the two subunits are joined together to form a single, larger functional protein complex. A small inset video in the bottom right corner shows a woman in a blue sari speaking. Logos for IIT Bombay and NPTEL are visible at the bottom right of the slide.

If we want to look at the protein-protein interface for drug design, we realize that there are not only different subunits of the proteins that form complexes to get to their functional forms, but there are also several other monomeric proteins that would be required to interact with each other to form a functional protein.

(Refer Slide Time: 10:17)

Protein – protein interface for drug design

- Structural information at the protein – protein interface provides foundations for rational drug design
- Peptide sequences could be designed that target the interface inhibiting complex formation



Functional protein

Interface

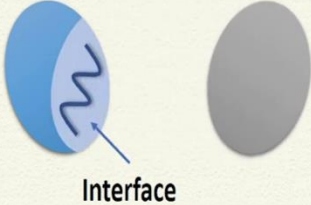
In this case what might happen is, the specific interface could be used for the development of drugs. So this is the structural information obtained from the protein-protein interface, which will provide fine foundations for rational drug design.

A knowledge of the residues that are present in the interface can be used for such an action and in this case if the interface is blocked, then the complex does not form the specific functional protein and the action cannot take place. So the peptide sequences can be designed, that target the interface that are going to inhibit complex formation.



(Refer Slide Time: 11:04)

Protein – protein interface for drug design

Peptide bound at the interface inhibits complex formation



Interface



So if we have the specific interface and we have a peptide that can bind at the interface, then once the peptide is bound at the interface this is going to prevent complex formation and will not result in a functional protein, thus inhibiting the specific activity it was performed to do. As this is not possible, we have no functional protein.



(Refer Slide Time: 11:32)

Protein – protein interface for drug design

Peptidomimetic:

- I. Identification of a tight binding potential peptide sequence
- II. Modification of the peptide to enhance stability, uptake and delivery

The modification of a natural peptide for higher stability and uptake potential that mimics the natural peptide by exploiting their binding mechanism is known as a peptidomimetic

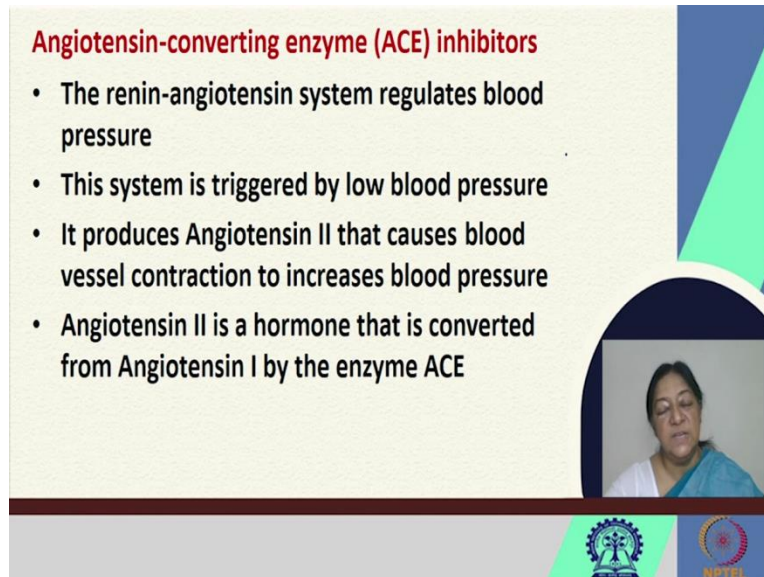


When we look at the protein-protein interface for drug design, we have what are called peptidomimetic structures. This identifies a tight binding potential peptide sequence, then there is modification of the specific peptide sequence to enhance stability uptake and delivery.

The modification of a natural peptide in many cases for higher stability and uptake potential, that actually mimics the natural peptide by exploiting the binding mechanism, is known as a

peptidomimetic as it is mimicking the peptide structure; it is mimicking the activity that the peptide was designed to do.

(Refer Slide Time: 12:22)



Angiotensin-converting enzyme (ACE) inhibitors

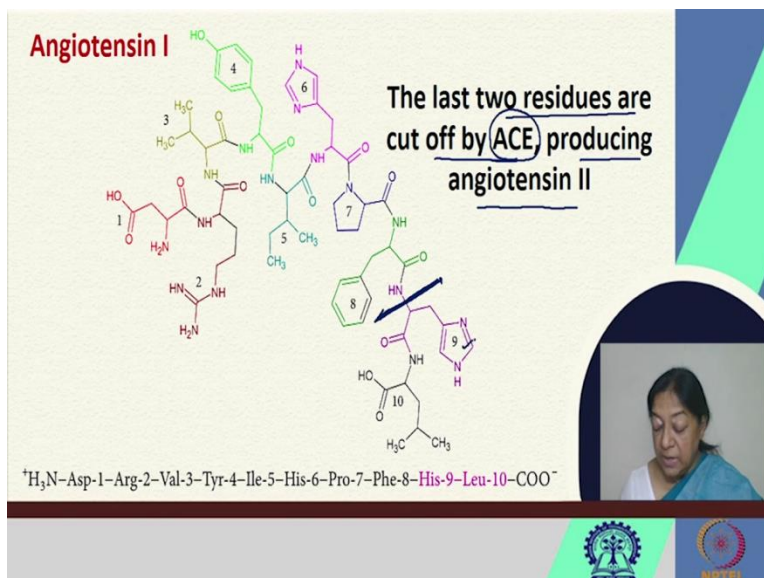
- The renin-angiotensin system regulates blood pressure
- This system is triggered by low blood pressure
- It produces Angiotensin II that causes blood vessel contraction to increase blood pressure
- Angiotensin II is a hormone that is converted from Angiotensin I by the enzyme ACE

The slide features a video inset of a woman in a blue sari. At the bottom, there are logos for a university and NPTEL.

We will look at a specific example to understand this concept. This is the angiotensin converting enzyme ACE inhibitors, designed for this enzyme that work as drugs, as medicine. A short background on this; this is the renin angiotensin system, that regulates blood pressure. The system is triggered by low blood pressure. What happens in this case, angiotensin II that causes blood vessel contraction is developed or is formed, so that there is an increase in blood pressure.

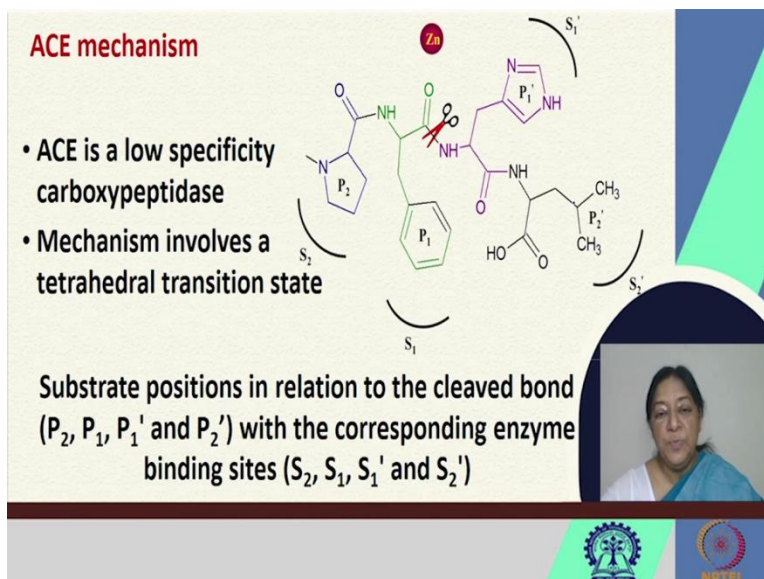
So, the system is triggered when there is low blood pressure. Angiotensin II is produced that results in blood vessel contraction, that in turn increases blood pressure. This angiotensin II is a hormone that is converted from angiotensin I, by the angiotensin converting enzyme ACE.

(Refer Slide Time: 13:36)



This [refer to slide] is angiotensin 1. The last two residues are cut off by this specific enzyme ACE, producing angiotensin II that then leads to blood vessel contraction and increase of blood pressure.

(Refer Slide Time: 13:57)

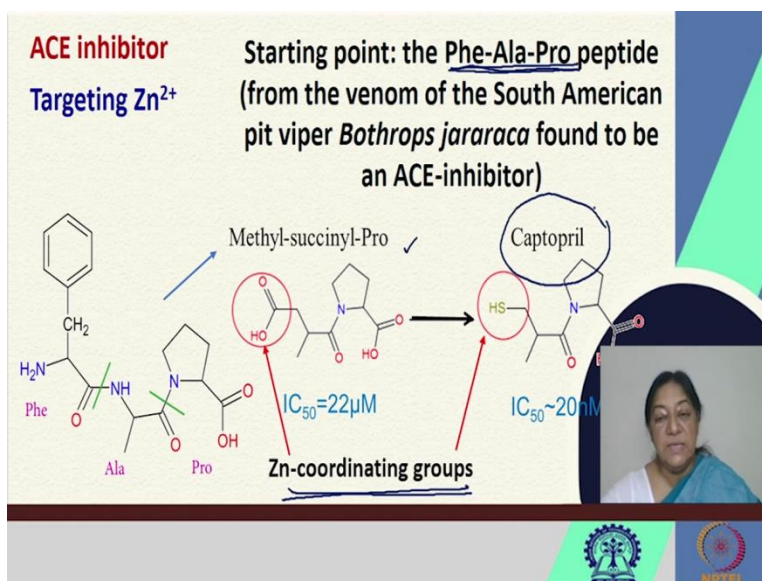


We look at this specific end of this peptide. The cleavage occurs at this position here, where there is a specific cleavage occurring that forms angiotensin II. The last two residues 9 and 10 are cleaved. This ACE thus, as we understand in our enzymatic terminology would be a carboxy peptidase, where it is cleaving the specific residues from the carboxyl end of the angiotensin I.

So, ACE is a low specificity carboxypeptidase and the mechanism involves a tetrahedral transition state. What is shown in the diagram [refer to slide] is the substrate positions in relation to the cleaved bond, that is this particular bond where we have the P_2, P_1, P_1' and the P_2' .

So, the P₁' and the P₂' are the ones that are cleaved and the P₂ and the P₁ are the ones that remain in angiotensin II and these are the specific substrate locations where there is the recognition, the binding of this specific peptide that is angiotensin I. There is also a zinc metal ion involved in the coordination sites, that is involved in the overall mechanism of the ACE enzyme.

(Refer Slide Time: 15:35)

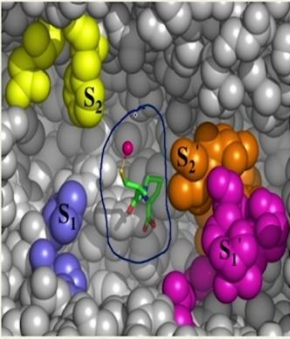


What we have therefore, is the design of an ace inhibitor. What can happen is, there can be targeting of specific sites. The targeting of the Zn²⁺ resulted from a starting point where a phenylalanine ala proline tripeptide was found to be an inhibitor of ACE.

So, this inhibitor was looked at from a structural point of view and what happened was specific zinc coordinated groups were attached to the moiety, to have a recognition of the sites, to see how they could be developed in a drug approach where we had a drug or there is a drug called captopril that works in this way, targeting the zinc.

(Refer Slide Time: 16:38)



ACE inhibitor
Targeting Zn²⁺



Captopril bound ACE

- Sulfhydryl group coordinating the zinc ion
- Methyl group occupying S₁'
- Prolyl group occupying S₂'

PDB ID: 1UZF

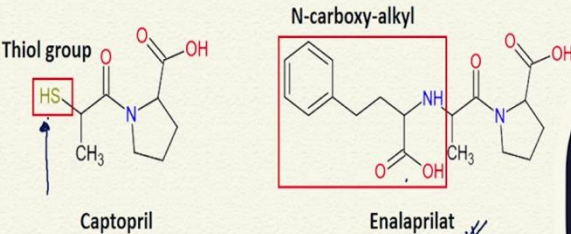



If we look at captopril bound ACE in this [refer to slide] structure, the sulfhydryl group coordinates the zinc ion, there is a methyl group that occupies the S₁' site and a prolyl group that occupies the S₂' site. So this is where it acts; the specific active site of this ACE bound to captopril.

(Refer Slide Time: 17:06)

ACE inhibitor
Targeting binding site S₁

- Modification of captopril to avoid side-effects (e.g. rash)
- Solution: non-SH inhibitor that binds S₁ with high affinity

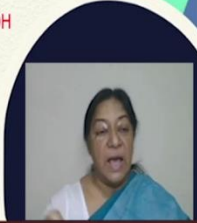



Thiol group

N-carboxy-alkyl

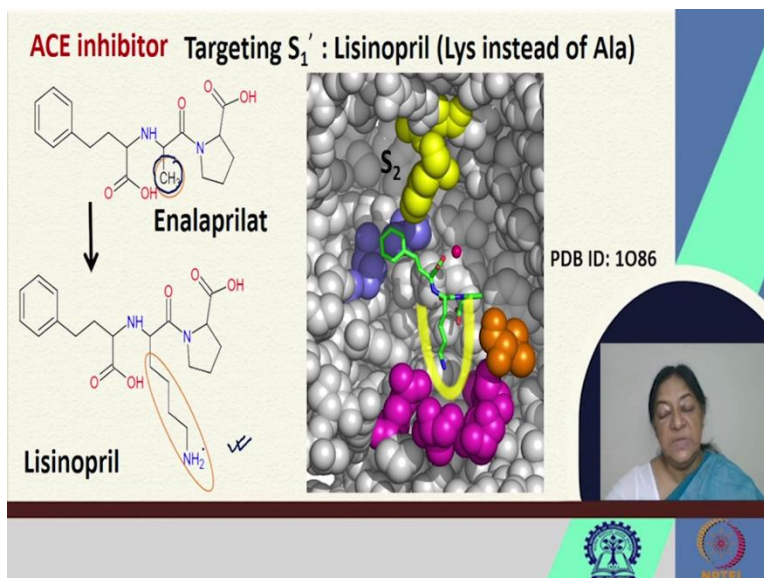
Captopril

Enalaprilat ✓

However, there were modifications of captopril required for avoiding some side effects for example like rashes. This indicated that there would have to be a development at a region other than the zinc binding site, where the S₁ site could also be targeted. The solution was to develop a non-SH inhibitor that bound to S₁ with high affinity. This resulted in the development of enalaprilat, which had the capability of binding to zinc, but did not have the thiol group present.

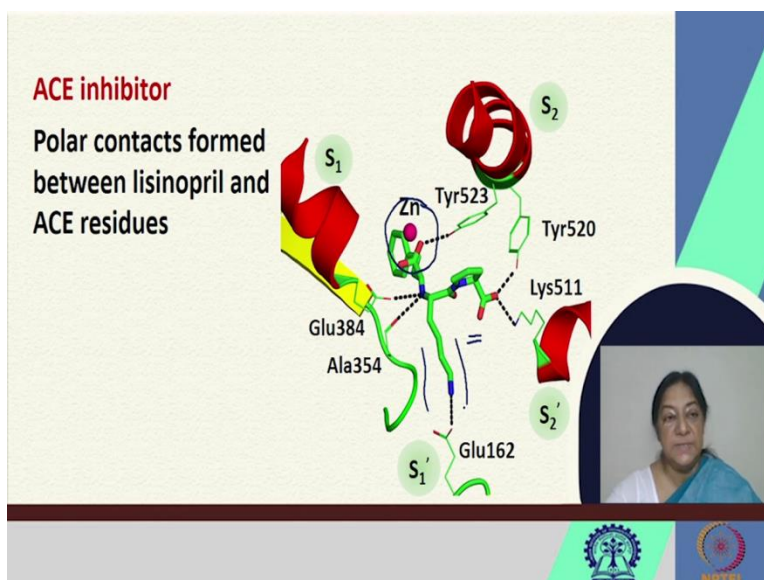
(Refer Slide Time: 17:51)



Further modifications led to the development of lisinopril, which had a lysine residue present here [refer to slide] in the active site of the protein, where this methyl group for alanine was replaced with a lysine group. In this case when the targeting offers specific interactions, that is where the design comes into the picture.

When we look at the specific design and how it can interact with the substrate residues, in this case the substrate being a peptide and the specific residues present in the protein, that is important in the design of such inhibitors of the protein.

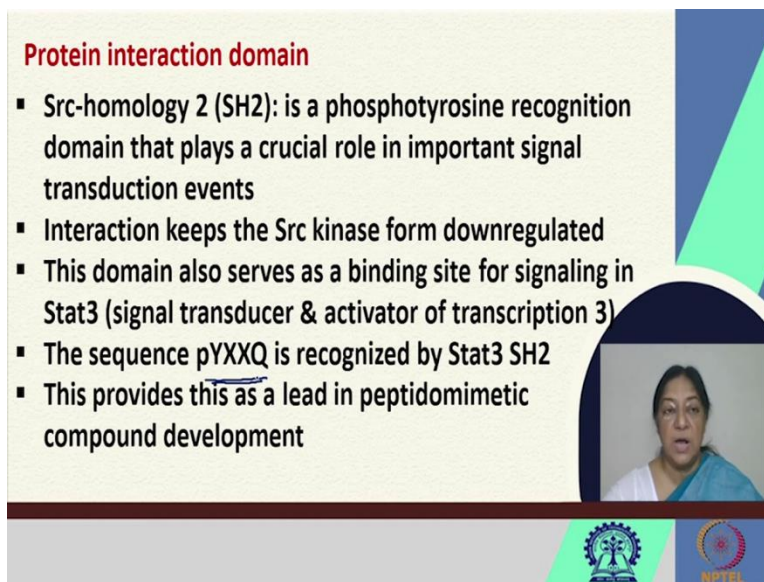
(Refer Slide Time: 18:43)



So looking [refer to slide] at the ace inhibitor what happened, the presence of the lysine resulted in greater polar contacts. There was the coordination with the zinc ion here, specific coordination sites that could occur with the prolyl residue and with the lysine residue, the formation of extra

polar contacts. All this goes into the design of an inhibitor. We learnt in our enzyme inhibition studies, how these can be determined and how the specific inhibition constants of these compounds determine from enzyme kinetic studies.

(Refer Slide Time: 19:32)



Protein interaction domain

- Src-homology 2 (SH2): is a phosphotyrosine recognition domain that plays a crucial role in important signal transduction events
- Interaction keeps the Src kinase form downregulated
- This domain also serves as a binding site for signaling in Stat3 (signal transducer & activator of transcription 3)
- The sequence pYXXQ is recognized by Stat3 SH2
- This provides this as a lead in peptidomimetic compound development

The slide features a light green background with a dark blue and light green geometric design on the right side. A small video inset in the bottom right corner shows a woman with dark hair wearing a blue sari. At the bottom of the slide, there are two logos: a circular emblem on the left and the acronym 'SPTTEL' on the right.

So when we look at the protein interaction domain, we revisit the Src-homology SH2. We found out that this is a phosphotyrosine recognition domain, that plays a crucial role in important signal transduction events. This interaction keeps the Src kinase form downregulated and the domain also serves as a binding site for a signaling stat3, that is a signal transducer and activator of transcription 3.




But without going into the details of this, the specific sequence, the peptide sequence is recognized by a domain. So this peptide sequence can now be modified, considering this as a lead in a peptidomimetic compound development for an effective drug.

(Refer Slide Time: 20:28)

Protein – protein interface for drug design

Modifications:

- Alteration of amino acids to nonnatural amino acids
- Cyclization of the peptide
- Constraining the peptide so that it forms an alpha helix



So these modifications that can occur, can result in the alteration of amino acids to non natural amino acids for better binding, for better affinity. There could be cyclization of the peptides. There are examples of cyclic peptide antibiotics, they could also be constraining the peptide like we saw in a stapled peptide, so that it forms a specific secondary structural unit. For example the alpha helix, that would fit into the binding pocket of the binding cleft, to result in better inhibition.

(Refer Slide Time: 21:07)

Peptide as therapeutics

- Currently the pharmaceutical market is mostly occupied by small-molecule drugs
- Challenges that this small-molecule drugs face
 - ✓ target specificity
 - ✓ cell membrane permeability






Looking at peptides as therapeutics, currently the pharmaceutical market is occupied with small molecule drugs, but the challenge of this is target specificity and cell membrane permeability.

(Refer Slide Time: 21:24)

Peptide as therapeutics

- Synthetic drugs for a specific target often encounter the problem of low bio-membrane permeability
- This hampers the systemic drug distribution and limits its therapeutic value



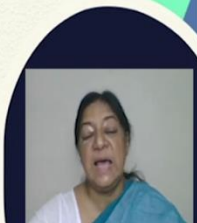


There are synthetic drugs available for a specific target, but what happens in most cases there is low bio-membrane permeability, which hampers systemic drug distribution and in turn limits its therapeutic value.

(Refer Slide Time: 21:42)

Peptide as therapeutics

- Peptides, on contrary, have high selectivity by means of their multiple points of contact with their target
- There are also specific sequences of peptide that are capable of penetrating cell membrane and having antimicrobial property
- Thus, this peptides can be utilized in therapeutics to increase the uptake efficiency of drugs, as antimicrobials, etc





Peptides on the contrary have higher selectivity because of their multiple points of contact with the target that is possible. There are also specific sequences of peptides, that are capable of penetrating cell membranes and have antimicrobial properties. Thus, these peptides can be utilized in therapeutics to increase the uptake efficiency of drugs as antimicrobials and so on.

(Refer Slide Time: 22:12)

Cell-penetrating peptides (CPPs)


- CPPs are peptides that are able to penetrate biological membranes
- They are short peptides (<30 amino acids long)
- Facilitates transport of the bioactive molecules into the cells



There are cell penetrating peptides that are able to penetrate biological membranes. These are short peptides and they facilitate the transport of bioactive molecules into the cells.


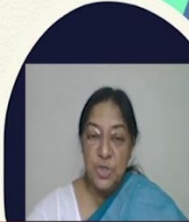
(Refer Slide Time: 22:31)

Cell-penetrating peptides (CPPs)



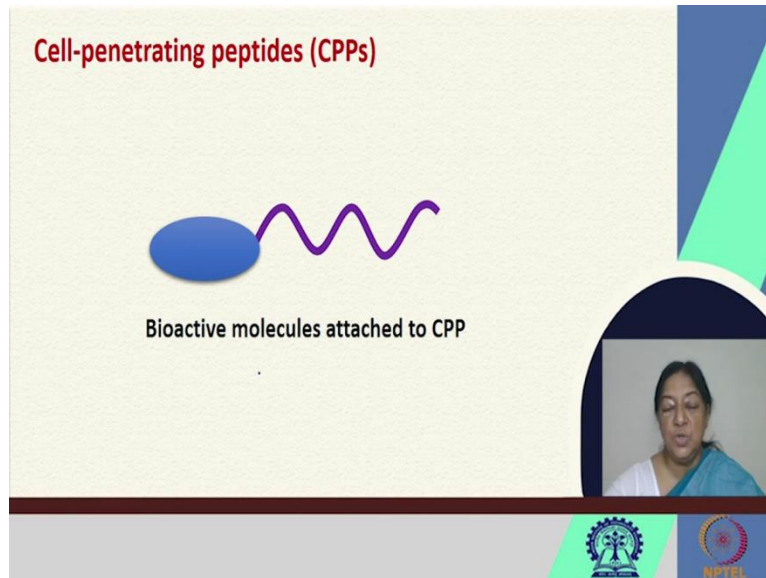
Bioactive molecules

Cell-penetrating peptides



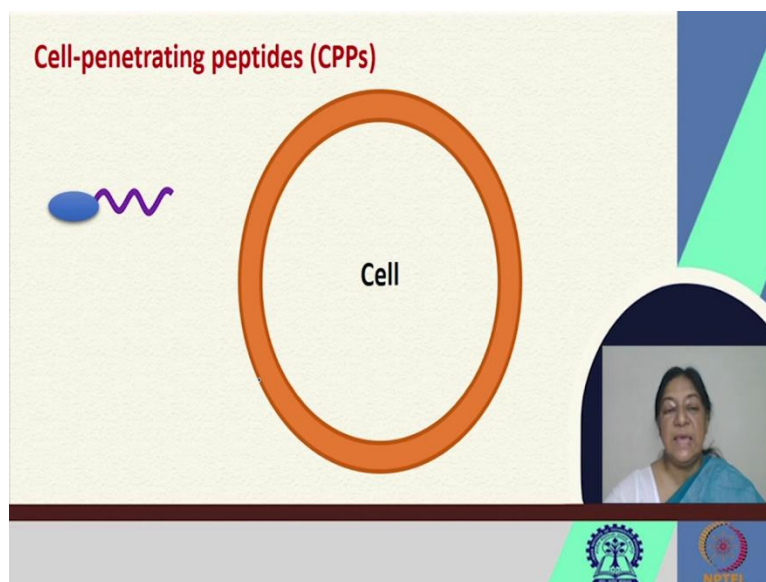
So these are also very interesting peptides that have a specific unit. If it is a cell penetrating peptide and there is a specific bioactive molecule that has to be transported inside the cell.

(Refer Slide Time: 22:44)



The bioactive molecule is attached to the CPP.

(Refer Slide Time: 22:49)



(Refer Slide Time: 22:54)

Cell-penetrating peptides (CPPs)

Transport and delivery of the bioactive molecule within the cell

Cytoplasm

The diagram illustrates a cell as a large orange oval. Inside the cell, a blue oval and a purple wavy line represent a bioactive molecule being transported. The word 'Cytoplasm' is written inside the cell. A small inset video in the bottom right corner shows a woman with dark hair wearing a blue sari, speaking. The background of the slide is light green with a blue and green geometric design on the right side. Logos for a university and NPTEL are visible at the bottom.

As this peptide can penetrate the cell, it allows the transport and the delivery of the bioactive molecule within the cell.

(Refer Slide Time: 23:01)

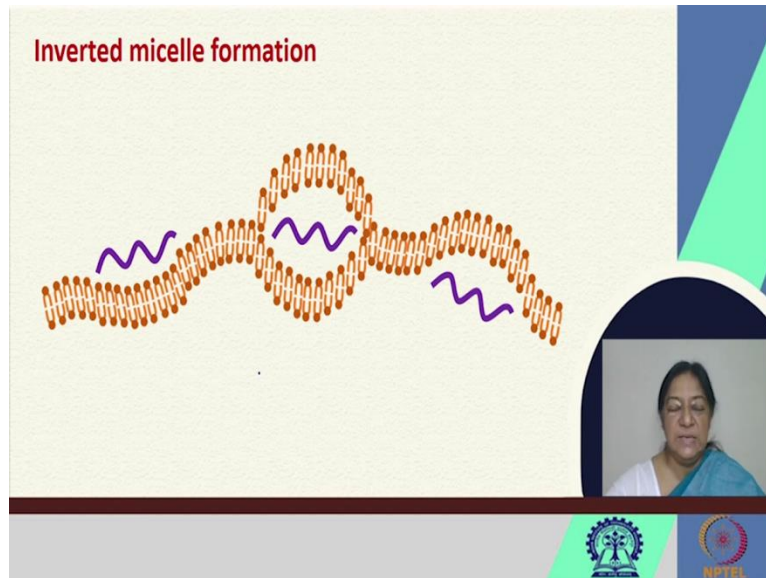
Mechanism of cellular uptake

- Direct penetration pathways
 - ✓ Inverted micelle formation
 - ✓ Carpet model
 - ✓ Pore formation
- Endocytosis pathways
 - ✓ Macropinocytosis
 - ✓ Endocytosis

The slide lists two main categories of cellular uptake mechanisms for CPPs. The first category is 'Direct penetration pathways', which includes 'Inverted micelle formation', 'Carpet model', and 'Pore formation'. The second category is 'Endocytosis pathways', which includes 'Macropinocytosis' and 'Endocytosis'. A small inset video in the bottom right corner shows the same woman from the previous slide speaking. The background and logos are consistent with the first slide.

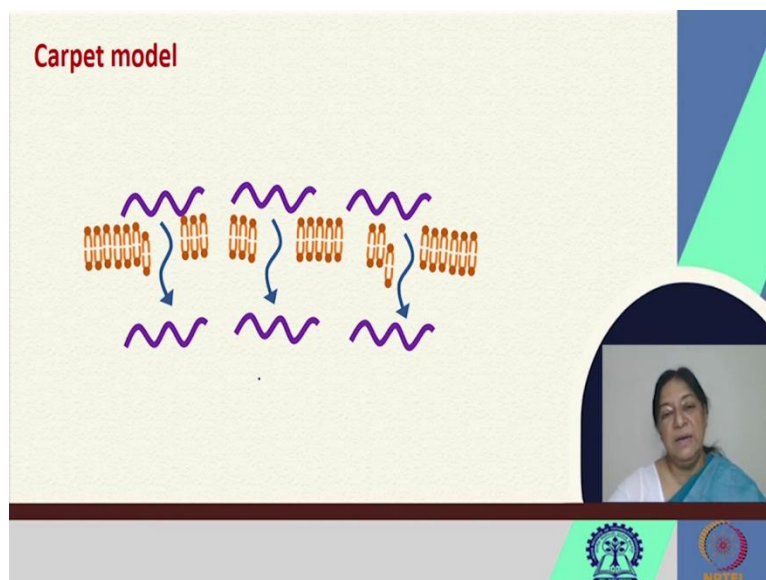
There are several methods by which this can occur, there is direct penetration or endocytosis pathways. We will just look at them from a point of view, understanding how they work.

(Refer Slide Time: 23:15)



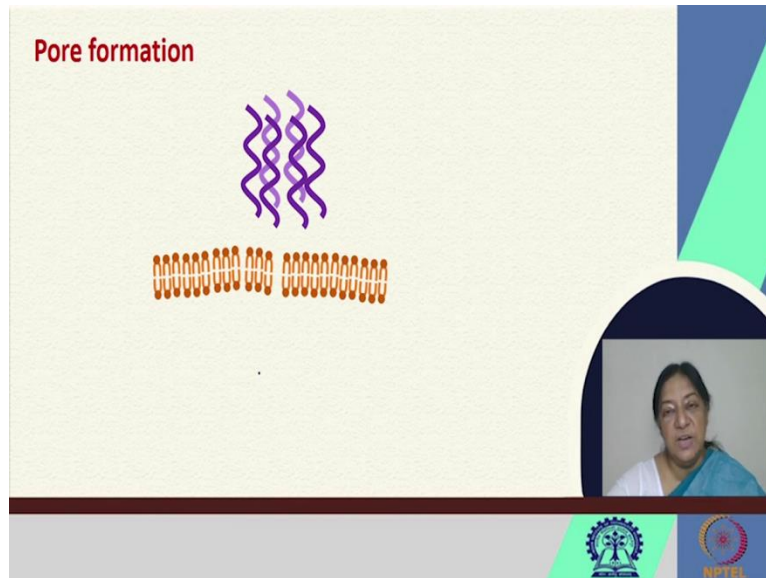
In an inverted micelle formation what happens is, there is the encapsulation of this peptide so to speak, that then transfers it from the outer part of the membrane inside the cell.

(Refer Slide Time: 23:30)



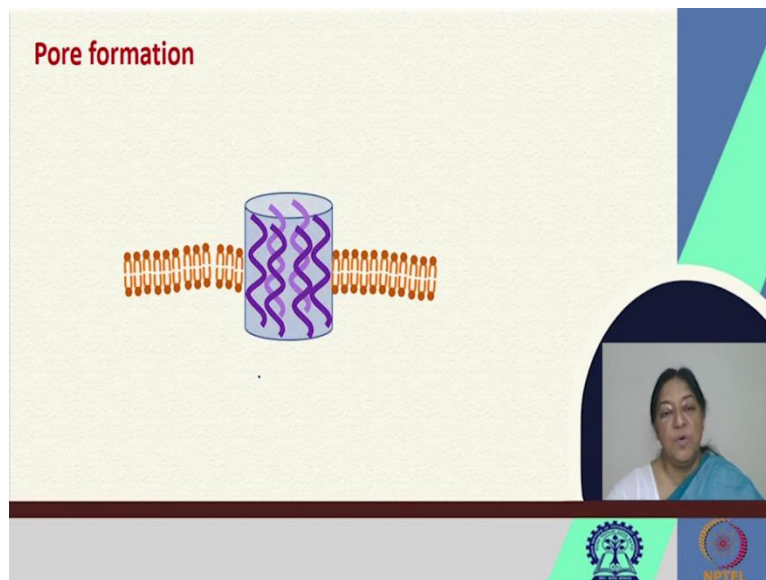
In a carpet model [refer to slide] there are coverages of the lipid bilayer, that have a movement that allow the transport.

(Refer Slide Time: 23:38)



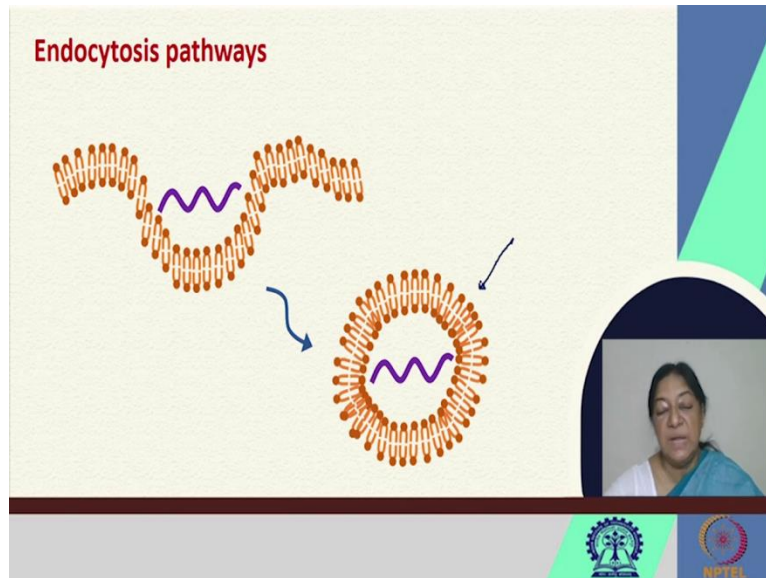
In the pore formation [refer to slide] these are triggered again by the movement of the fluid membrane that we know, the leaflet of the membrane, allowing the transport of biomolecules.

(Refer Slide Time: 23:45)



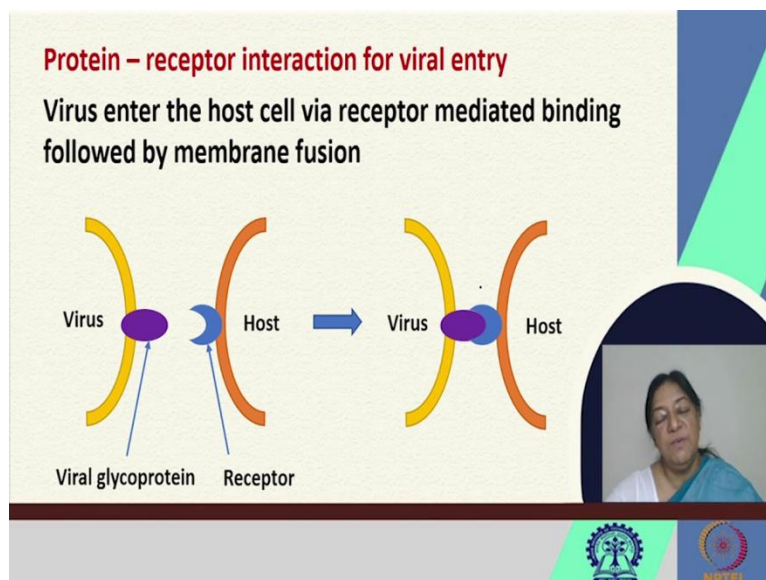
So we understand that the interactions of these peptides with the membranes is crucial for this specific formation to occur.

(Refer Slide Time: 24:08)



In the endocytosis pathways [refer to slide] there are methods by which there are formations of such entrapped or encapsulated peptides, that are then transferred within the cell.

(Refer Slide Time: 24:23)



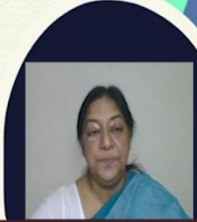


If we look at protein receptor interaction for viral entry, we know that the virus has to enter the host cell via again a receptor mediating binding, followed by membrane fusion. So in this case [refer to slide] there is a host and there is the virus and there is a specific glycoprotein that is present on the virus surface and there is a receptor that has a specific recognition site. Then there is the interaction that allows the virus to get into contact with the host.

(Refer Slide Time: 25:05)

Peptide inhibiting viral entry

- Studying the sequence involved in receptor binding and the mechanism of binding, peptide sequence are developed to inhibit receptor binding
- Peptide sequence mimicking the sequence involved in receptor binding can be employed
- Enfuvirtide is a 36-amino acid peptide developed as an HIV fusion inhibitor.






There are peptides that have been designed to inhibit this viral entry and by studying the sequence that is involved in the receptor binding and the mechanism of binding, the peptide sequence can be developed to inhibit the receptor binding. In turn the virus will not be able to attack the host. So the peptide sequence can mimic the sequence involved in receptor binding and that can be employed to prevent this process. For example enfuvirtide, a 36-amino acid peptide has been developed as an HIV fusion inhibitor.

(Refer Slide Time: 25:48)

Protein-peptide interactions

- Protein – protein interactions are crucial for many cellular processes
- Disruption of these interactions causes inhibition of their actions
- A good way to inhibit or regulate their action is to target specific protein – protein interactions
- Protein – peptide interaction finds applicability as therapeutics



When we look at protein peptide interactions, that are a subset of protein-protein interactions, we realize they are crucial for many cellular processes and disruption of these interactions causes inhibitions of their specific actions. A good way to inhibit or regulate their action is to target specific protein-protein interactions and we saw how protein peptide interactions find applicability as specific therapeutics.

(Refer Slide Time: 26:20)

Detection methods

How does ligand binding change protein conformation ?

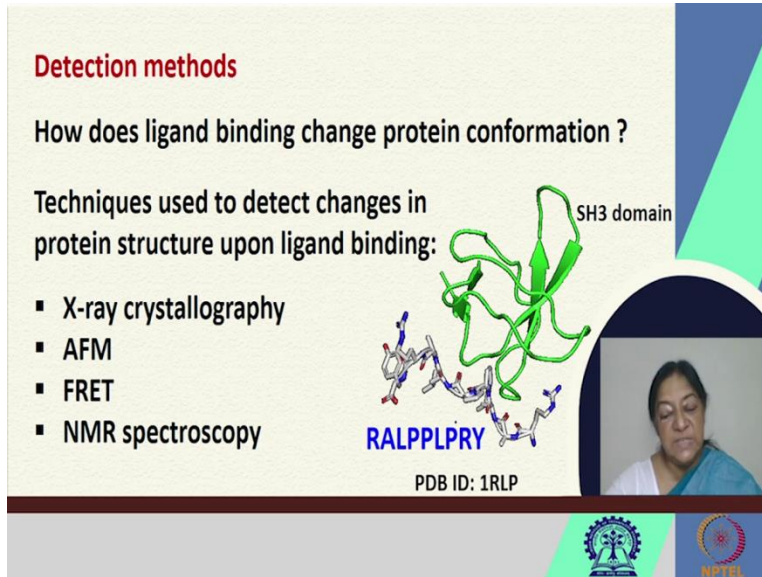
Techniques used to detect changes in protein structure upon ligand binding:

- X-ray crystallography
- AFM
- FRET
- NMR spectroscopy

RALPPLPRY

PDB ID: 1RLP

SH3 domain



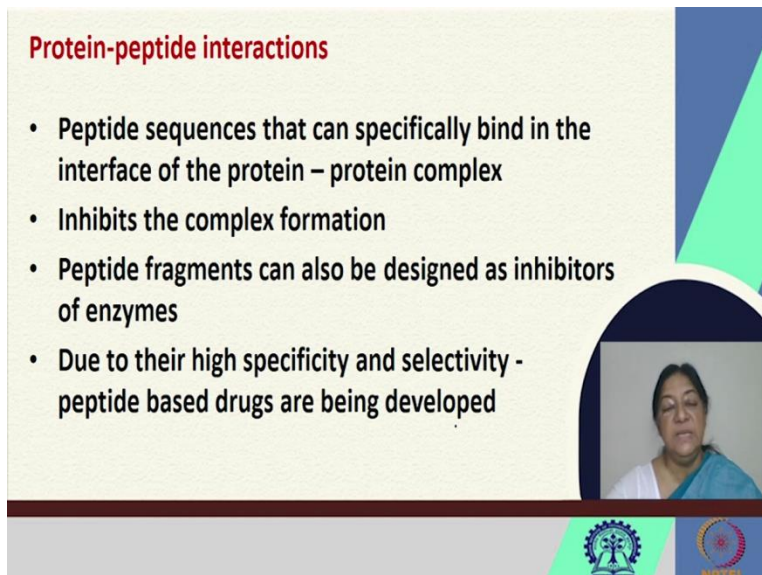
The slide features a light green background with a blue and green geometric design on the right. It contains a list of four detection methods: X-ray crystallography, AFM, FRET, and NMR spectroscopy. To the right of the list is a 3D molecular model of a protein structure. A green ribbon represents the SH3 domain, and a blue ribbon represents the peptide sequence RALPPLPRY. Below the peptide sequence, the PDB ID 1RLP is noted. A small circular inset in the bottom right corner shows a woman with dark hair, wearing a blue and white sari, speaking. At the bottom of the slide, there are logos for IIT Bombay and NPTEL.

There are specific detection methods to know how ligand binding changes the protein conformation. There are several detection methods that can be used. X-ray crystallography, AFM, FRET or NMR spectroscopy, depending upon the type of interaction that is being studied. These detection methods are going to lead us to better peptide mimetics, to better understanding of our protein-protein interfaces and protein-peptide interfaces.

(Refer Slide Time: 26:58)

Protein-peptide interactions

- Peptide sequences that can specifically bind in the interface of the protein – protein complex
- Inhibits the complex formation
- Peptide fragments can also be designed as inhibitors of enzymes
- Due to their high specificity and selectivity - peptide based drugs are being developed



The slide features a light green background with a blue and green geometric design on the right. It contains a bulleted list of four points regarding protein-peptide interactions. A small circular inset in the bottom right corner shows the same woman from the previous slide speaking. At the bottom of the slide, there are logos for IIT Bombay and NPTEL.

A knowledge of the peptide sequences that can specifically bind in the interface of the protein-protein complex, will help us to design inhibitors of enzymes that are going to inhibit the complex formation and because of their high specificity and selectivity, these peptide based drugs are being developed.

(Refer Slide Time: 27:23)

REFERENCES

- doi: 10.1016/0959-440x(95)80015-s
- <http://dx.doi.org/10.5772/48418>
- Kessel and Ben-Tal, Introduction to Proteins: Structure, Function, and Motion: 2nd Ed (2018)

The slide features a video inset in the bottom right corner showing a woman with dark hair wearing a blue and white sari. At the bottom of the slide, there are two logos: the IIT Bombay logo on the left and the NPTEL logo on the right. The background of the slide is light green with a dark blue header and footer.

These [refer to slide] are the references.

Thank you.