Comparative *in silico* docking of bioactive peptides across the gut-skin axis: A systems approach to psoriasis modulation via the host-microbe interactions

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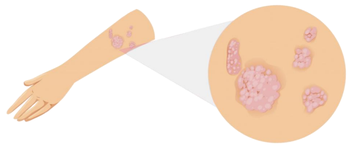
BACKGROUND

Psoriasis



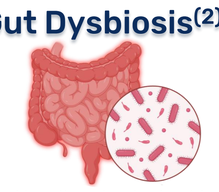
Immune-mediated inflammatory condition

Marked by keratinocyte hyperproliferation with activation of Th1/Th17 cells and elevated levels of cytokines such as TNF-α, IL-17, and IL-23.(1)

THE GUT-SKIN AXIS

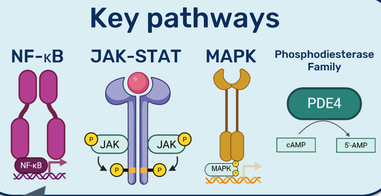
THERAPEUTIC POTENTIAL ?

Gut Dysbiosis(2)



Marked by altered gut microbiome composition, metabolite production, epithelial permeability, and activation of immune and inflammatory pathways

Key pathways

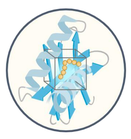


Bioactive peptides (BPeps)

Reported biological activities(2):

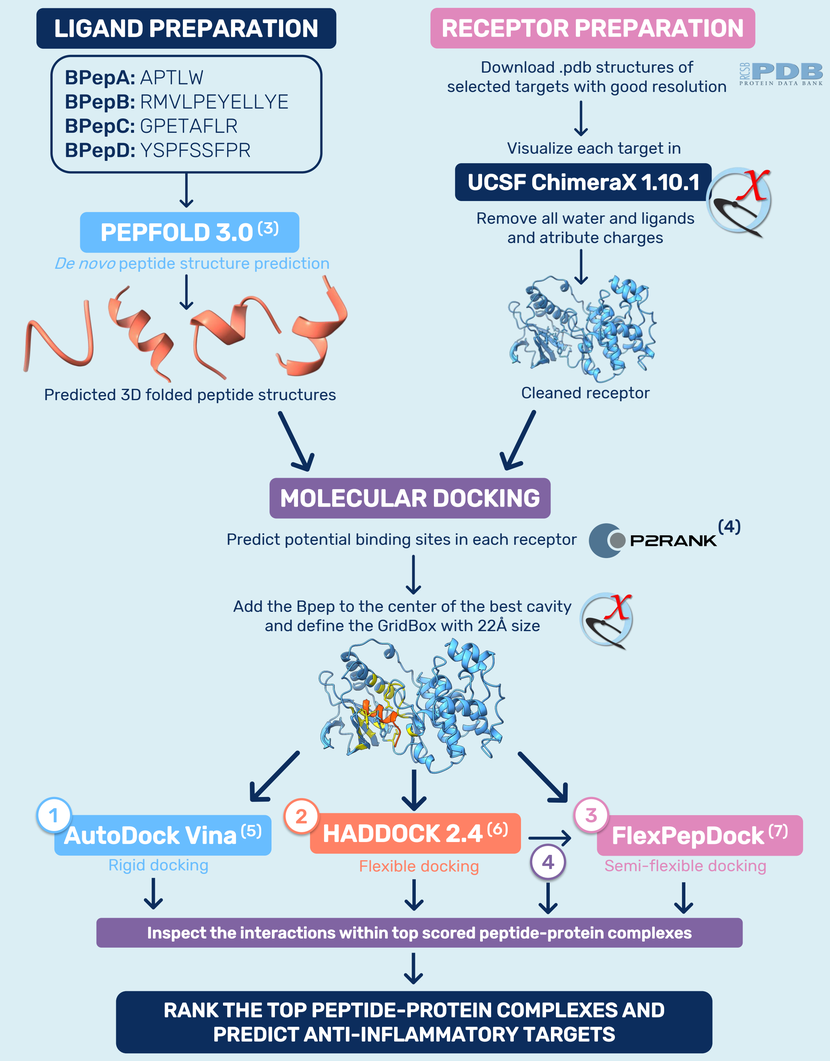
- Anti-inflammatory/ Immunomodulatory activity;
- Modulation of microbial diversity and metabolite production;
- Epithelial barrier function.

Can BPeps interact with key molecular targets involved in psoriasis and Inflammatory Bowel Disease?

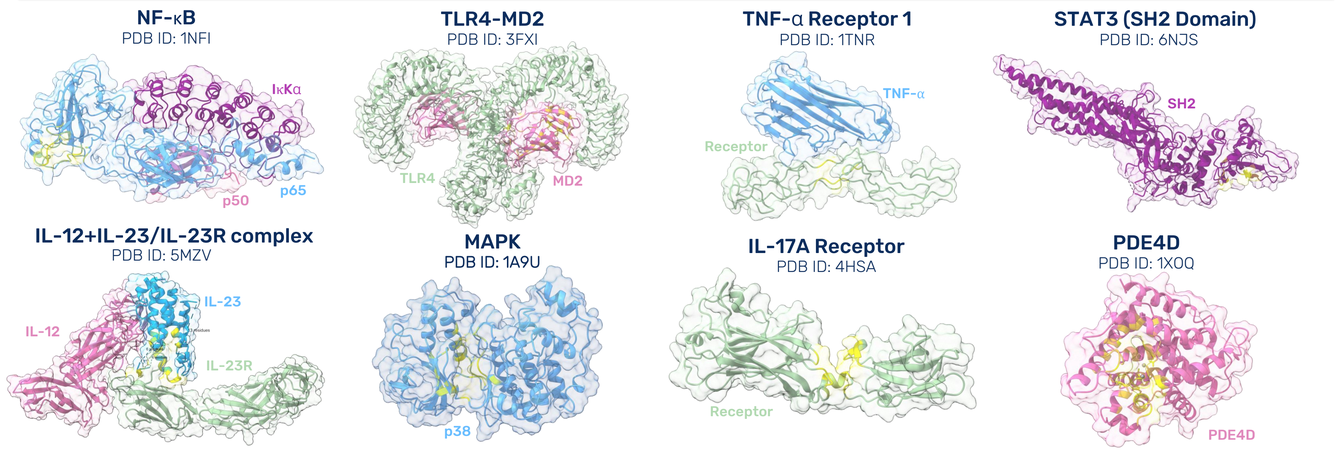


***In silico* anti-inflammatory activity prediction**
Molecular Docking

METHODOLOGY



SELECTED TARGETS AND PREDICTED BINDING SITES



Graphical representation of the selected targets for protein docking based on four major pathways: NF-κB, JAK-STAT, MAPK and PDE4. All structures were obtained from Protein Data Bank (PDB) and the predicted binding sites were obtained using P2Rank and are represented with yellow coloring. All representations were generated with UCFS ChimeraX 1.10.1 software.

RESULTS | DOCKING SCORES

1 AutoDock Vina

	BPepA	BPepB	BPepC	BPepD
NF-κB complex	-6.90	-5.60	-6.50	-6.50
TLR4-MD2	-9.70	-7.00	-9.80	-10.20
TNFα-R	-8.60	-7.20	-8.50	-9.00
STAT3-SH2	-6.60	-5.30	-6.50	-6.30
IL-23 / IL-23R	-7.80	-5.80	-7.30	-8.00
MAPK (p38)	-9.00	-2.50	-8.20	-7.80
IL-17A / IL-17RA	-8.50	-4.40	-7.50	-8.30
PDE4D	-10.00	10.10	-7.80	-7.40

Top complex: TLR4-MD2 + BpepD
Results: prioritizes smaller ligands with lower flexible torsions. This tool is not the most suitable for peptides.

3 FlexPepDock (centered on binding site)

	BPepA	BPepB	BPepC	BPepD
NF-κB complex	-122	-99.28	-149	-106
TLR4-MD2	-296	-137	-315	-265
TNFα-R	-229	-211	-243	-257
STAT3-SH2	-590	-56.73	-716	-465
IL-23 / IL-23R	-581	-595	-598	-568
MAPK (p38)	-522	-514	-525	-522
IL-17A / IL-17RA	-77.00	-117	-76.95	-64.22
PDE4D	-890	436	-904	-801

Top complex: PDE4D + BPepC
Results: lower quality complexes, with less negative scores. This tool is more adequate for refinement.

2 HADDOCK 2.4

	BPepA	BPepB	BPepC	BPepD
NF-κB complex	-51.3	-105.4	-62.9	-70.5
TLR4-MD2	-62.3	-72.9	-61.4	-65.5
TNFα-R	-56.3	-76.1	-58.6	-74.6
STAT3-SH2	-48.3	-82.7	-64.3	-60.4
IL-23 / IL-23R	-48.2	-59.4	-55.4	-62.4
MAPK (p38)	-66.9	-67.4	-76.0	-90.3
IL-17A / IL-17RA	-60.0	-73.2	-67.4	-97.7
PDE4D	-84.8	-90.1	-101.8	-100.9

Top complex: NF-κB + BPepB
Results: better scores for longer Bpeps. This tool is preferable for peptide-protein docking but is ambiguous so it requires refinement.

4 FlexPepDock (refined HADDOCK top position)

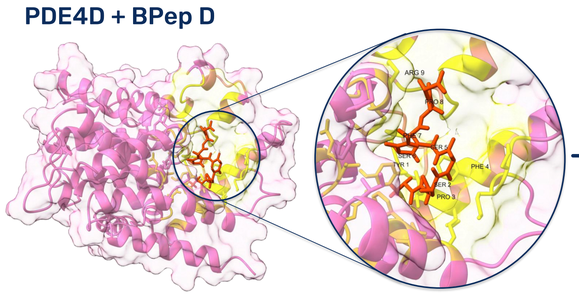
	BPepA	BPepB	BPepC	BPepD
NF-κB complex	-338	-399	-458	-292
TLR4-MD2	-360	-444	-516	-423
TNFα-R	-258	-211	-243	-257
STAT3-SH2	-424	-449	-457	-435
IL-23 / IL-23R	-481	-489	-483	-441
MAPK (p38)	-435	-401	-524	-417
IL-17A / IL-17RA	-45.36	12.21	-32.33	26.68
PDE4D	-720	-727	-608	-731

Top complex: PDE4D + BPepD
Results: more stable complexes when compared to the results with the Bpep centered on the binding site. Better approach to perform peptide-protein docking.

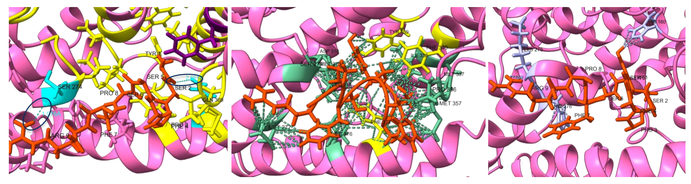
Main conclusion: The best approach for this kind of peptide-protein docking is to refine the top HADDOCK complex with FlexPepDock. The top three complexes based on this method are PDE4D+BPepD, TLR4-MD2 + BPepC, and IL-23/IL23R + BPepB.

RESULTS | TOP PEPTIDE-PROTEIN INTERACTIONS

PDE4D + BPep D



Key residues interacting with roflumilast (reported inhibitor): Asp318, Leu319, Trp332, Ile336, Met357, Gln369, Phe372

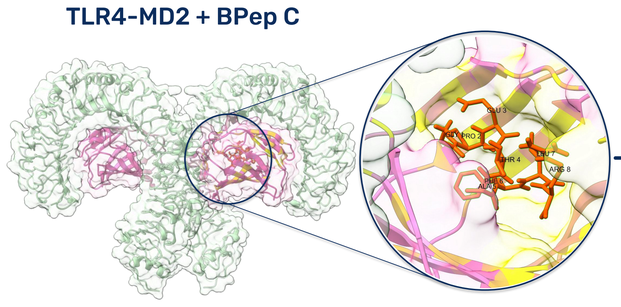


2 H-bonds found: Ser247, Gln369

Hydrophobic interactions: Tyr159*, Met273, Ser274, Met277, Asp318, Leu319, Ile336, Met337, Phe340*, Pro356, Met357, Phe372* *aromatic interactions

Eletrostatic / Salt Bridges: His160, Lys275, His276

TLR4-MD2 + BPep C



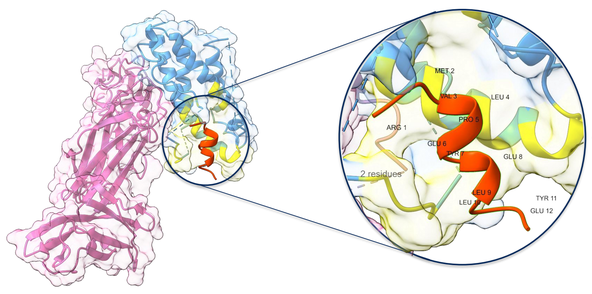
Key residues interacting with LPS: Leu61, Ile63, Tyr65, Leu71, Phe76, Leu74, Val82, Leu87, Ile94, Phe104, Ile117, Ser118, Phe119, Phe121, Ile124, Phe126, Lys122, Cys133, Tyr131, Val135, Phe147, Phe151

2 H-bonds found: Tyr102, Cys133

Hydrophobic interactions: Val48, Ile52, Leu61, Leu78, Ile94, Ile117, Val135, Ile153

Aromatic interactions: Phe76, Tyr102, Phe119, Phe121, Phe126, Phe147, Phe151

IL-23/IL-23R + BPep B



Key residues of IL-23 interacting with its receptor: Met54, Asp55, Arg57 Glu58, Trp156, Lys164

3 H-bonds found: Glu59, Asp67,Gln157

Hydrophobic interactions: Leu56, Val68, Phe99*, Leu103, Trp156*, Leu160, Leu161, Phe163*, Ile165 *aromatic interactions

Eletrostatic / Salt Bridges: Arg57, Glu58,Lys164

CONCLUSIONS AND FUTURE PERSPECTIVES:

- HADDOCK 2.4 followed by FlexPepDock is the most robust workflow for flexible peptide–protein docking.
- The top complexes are PDE4D–BPepD, TLR4–MD2–BPepC, and IL-23/IL-23R–BPepB.
- BPepD mimics roflumilast interactions with PDE4D; BPepC blocks the MD2–LPS pocket; BPepB engages IL-23 and may disrupt IL-23R binding.
- Molecular dynamics simulations are needed to assess complex stability and solvent effects.
- *In vitro* validation with advanced models and reference modulators is essential to confirm BPeps' anti-inflammatory potential.

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