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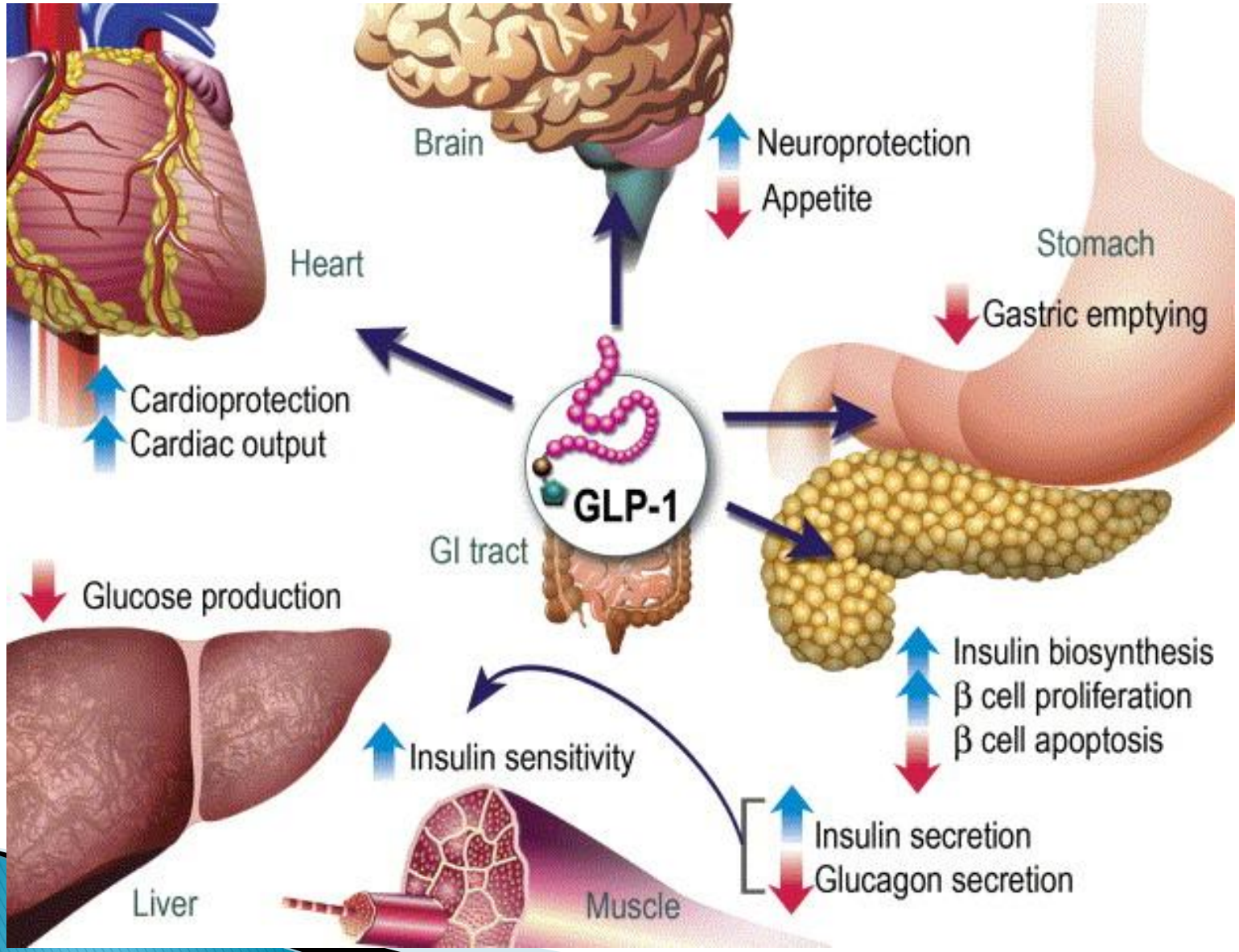
Molecular basis of drug action at the glucagon-like peptide 1 receptor

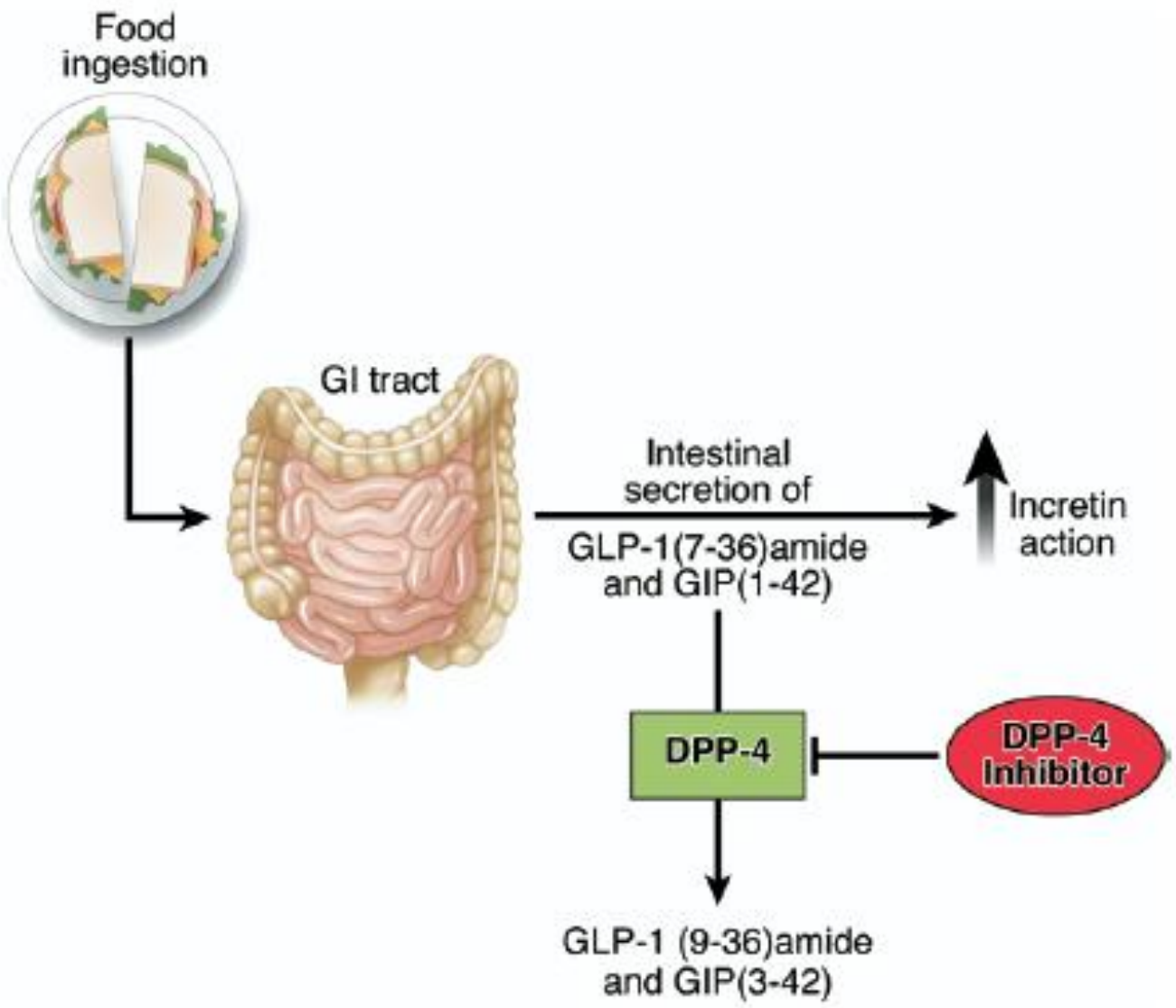
Maoqing Dong, M.D., **Ph.D.**

Associate Professor of Medicine, Dept. of Gastroenterology

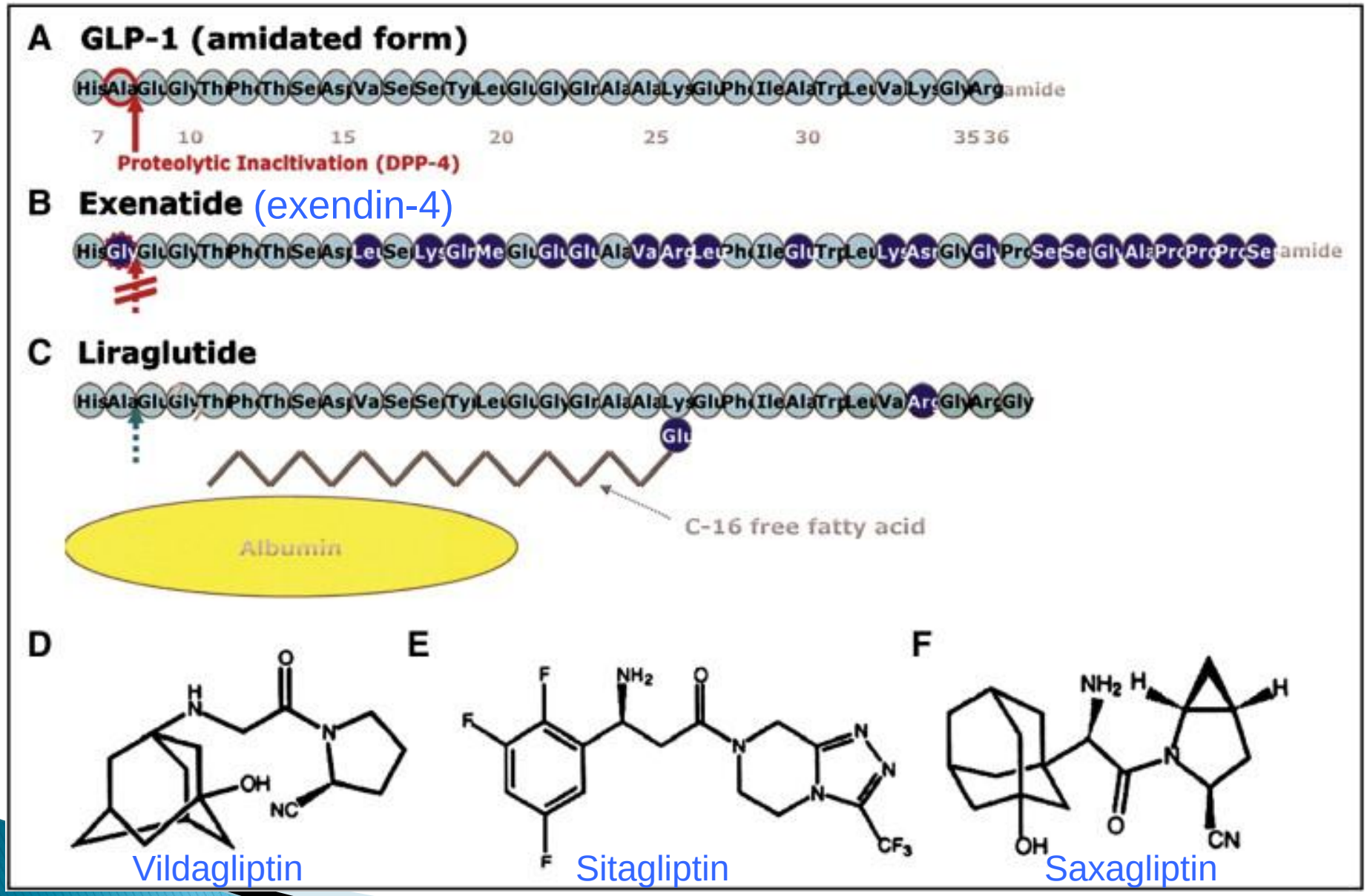
GLP-1 (glucagon-like peptide 1) and its antidiabetic actions



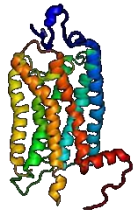
GLP-1 secretion and regulation



Incretin-based drugs for type 2 diabetes

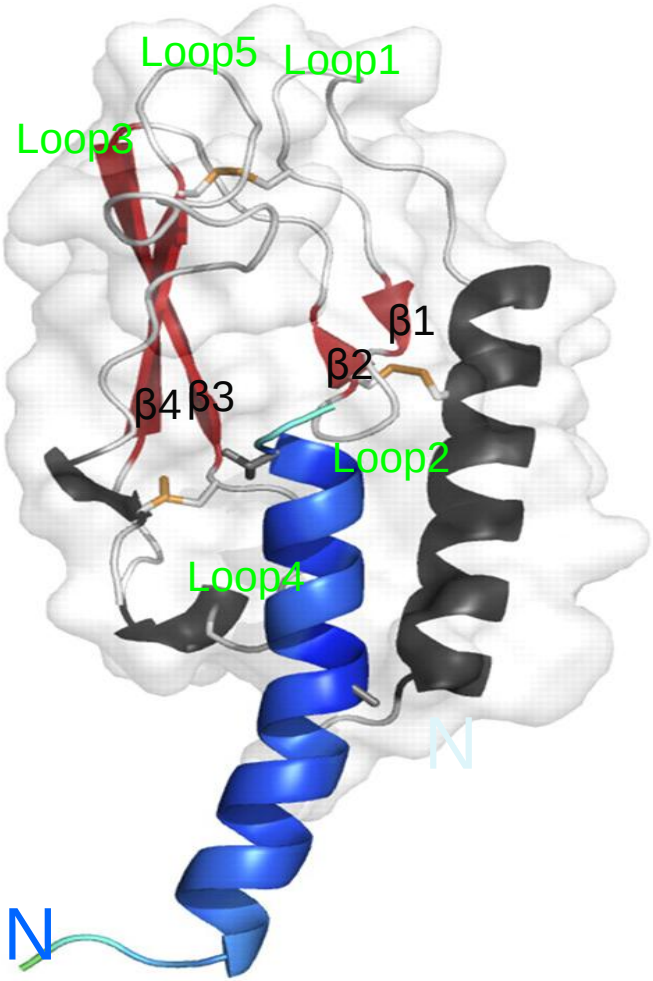


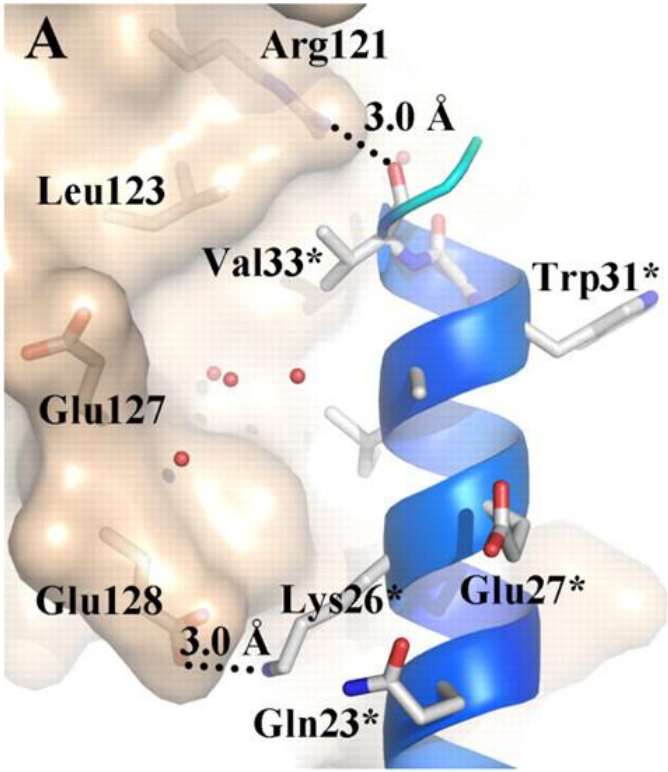
GLP-1 receptor

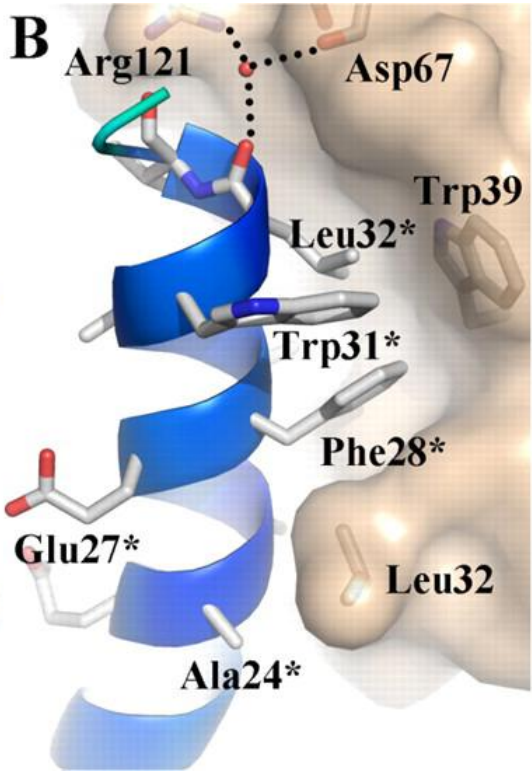


- GPCRs are the largest group of membrane receptors with seven transmembrane domains and represent targets for ~30% of market drugs.
- The GLP-1 receptor is a member of the Family B GPCRs, representing an important drug target for treatment of type 2 diabetes.
- This family is characterized by a long extracellular N-terminal domain (ECD), a predominant binding pocket for natural peptide ligand.
- Crystal structure of the ECD of the GLP-1 receptor has recently been reported (Underwood, et al., 2010). Little is known about how GLP-1 binds and activates its intact receptor.
- Understanding of the molecular basis of ligand binding and activation of the intact GLP-1 receptor **will** facilitate the development of new therapeutic drugs that can target not only this receptor, but also other members of the Family B GPCRs.

Crystal structure of GLP1-bound ECD of the GLP-1 receptor

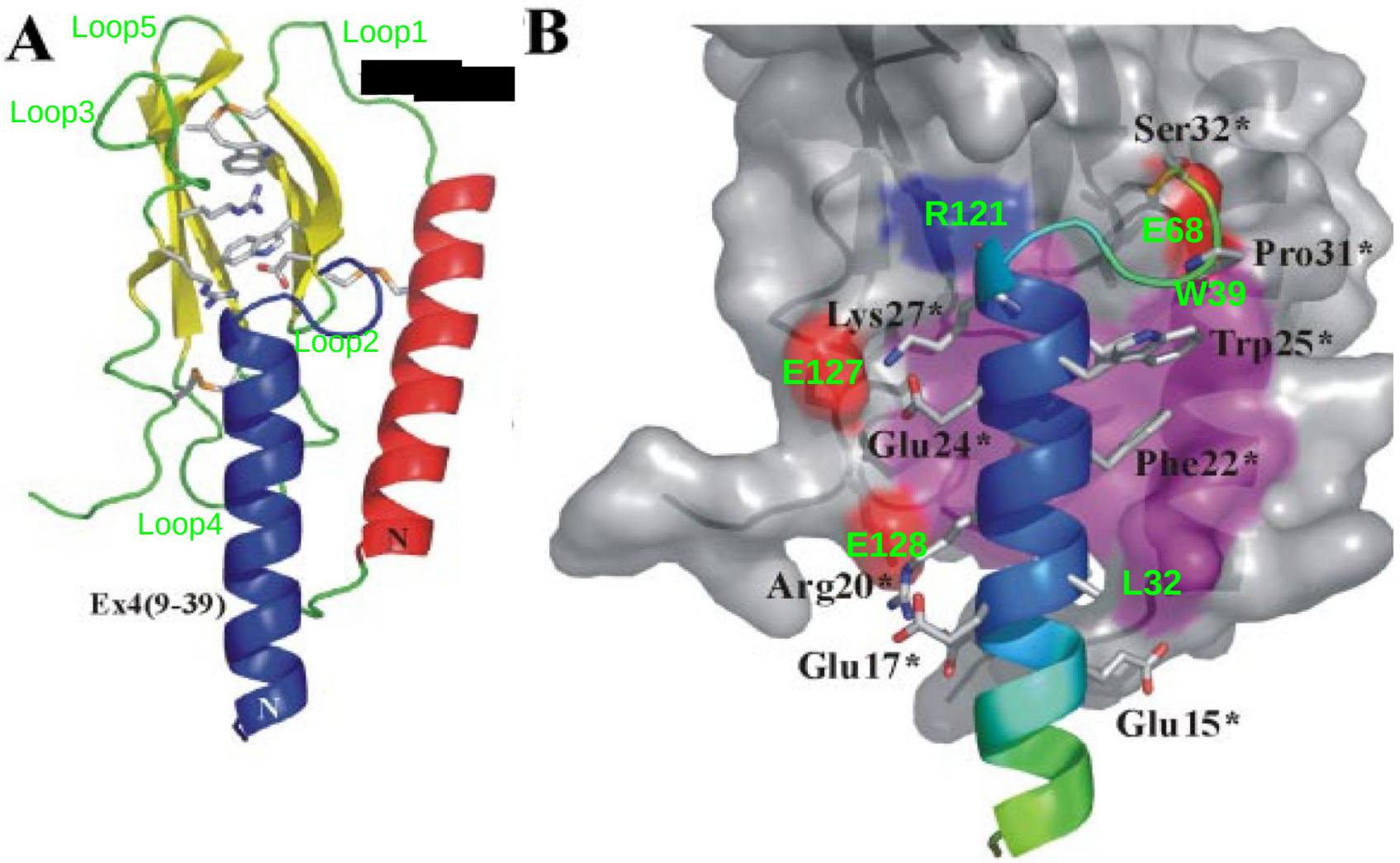






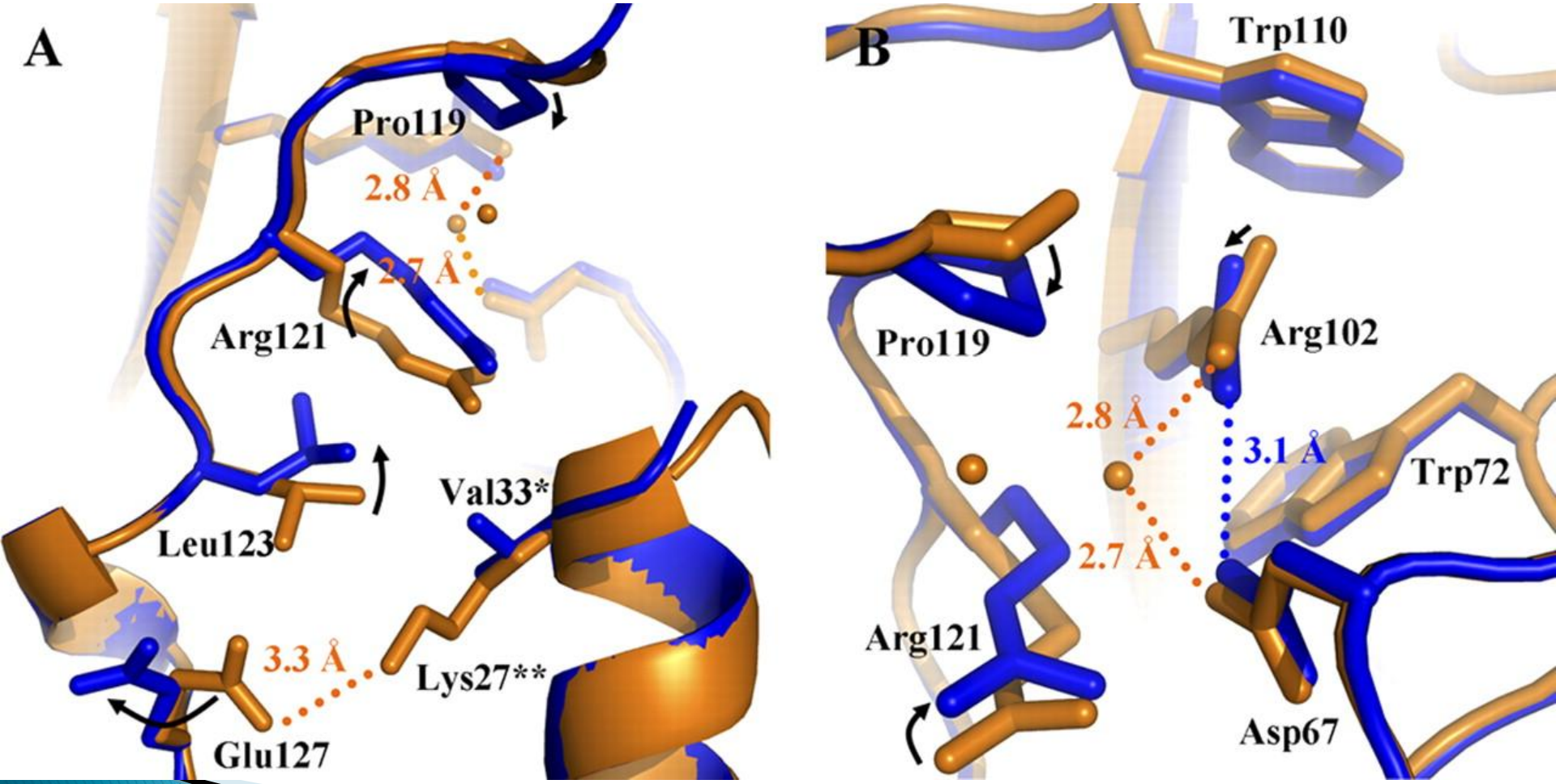
Underwood, et al., 2010

Crystal structure of antagonist-bound ECD of the GLP-1 receptor



Runge, et al., 2008

Differences between the GLP-1 and exendin-4(9-39)-bound ECD



Underwood, et al., 2010

Approaches to elucidation of the molecular mechanisms for binding and activation of Family B GPCRs

- Extend understanding of structure-activity relationships for peptides and receptors in this family
  - Mutagenesis
  - Chimeric analysis
  - Cross-chimeric analysis

- Expand structural insights into ligand-receptor complex
  - Photoaffinity labeling – residue-residue approximations
  - Fluorescence approaches (quenching, anisotropy, BRET, FRET) – conformation dynamic changes
  - Molecular modeling – sequential refinement

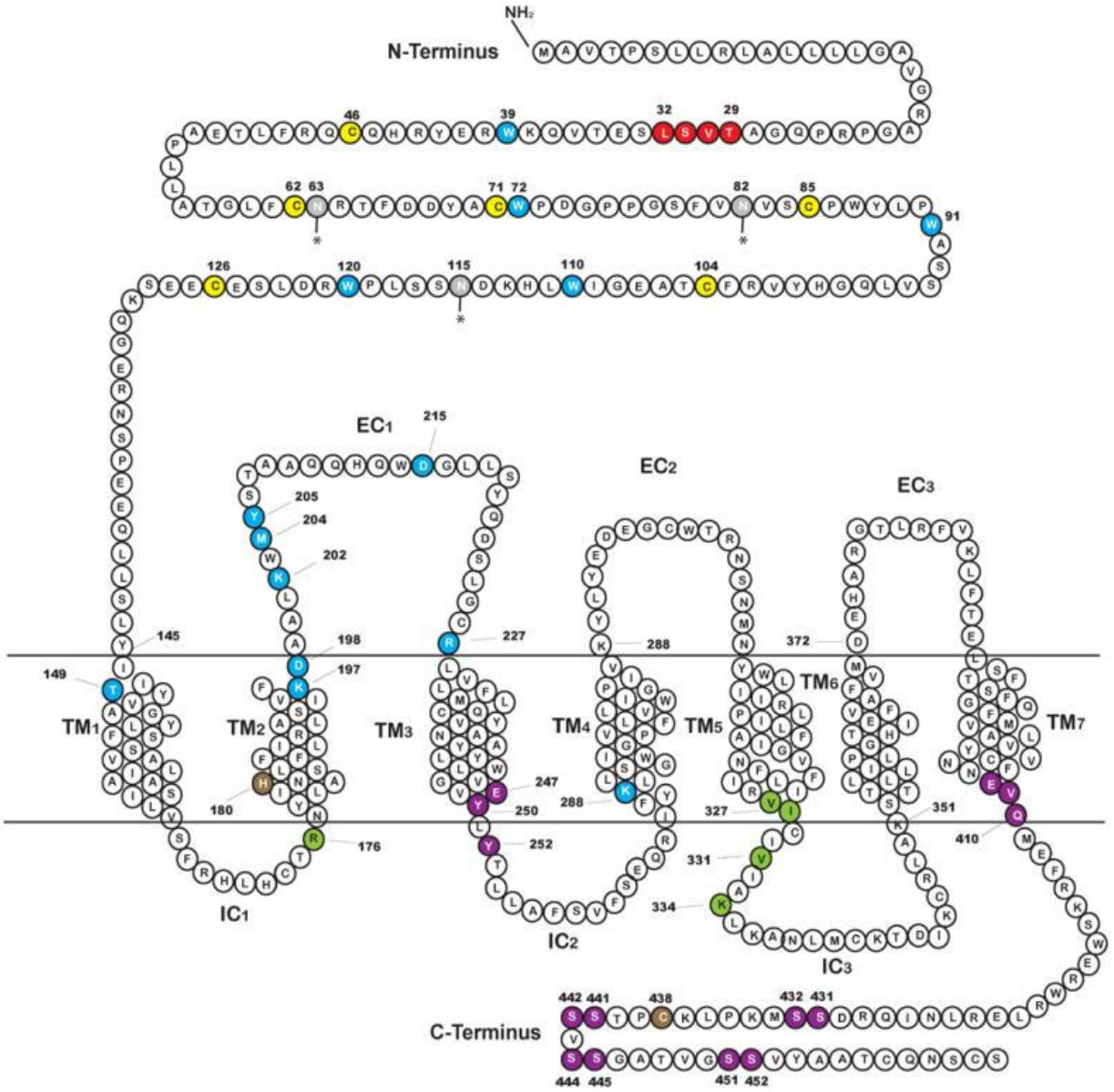
Current understanding of the mechanisms of ligand binding and activation of the GLP-1 receptor

- Receptor mutagenesis studies have identified that the GLP-1 receptor ECD is critical for GLP-1 binding. This is confirmed by high-resolution crystal structure.

- Inconsistencies in the absolute structures and ligand docking are present in the reported high-resolution structures of Family B GPCR ECDs. All structures used truncated ECD.

- The precise residues within the intact GLP-1 receptor that interact with the natural agonist, GLP-1, have not been experimentally mapped.

Functionally important residues within the GLP-1 receptor determined by mutagenesis

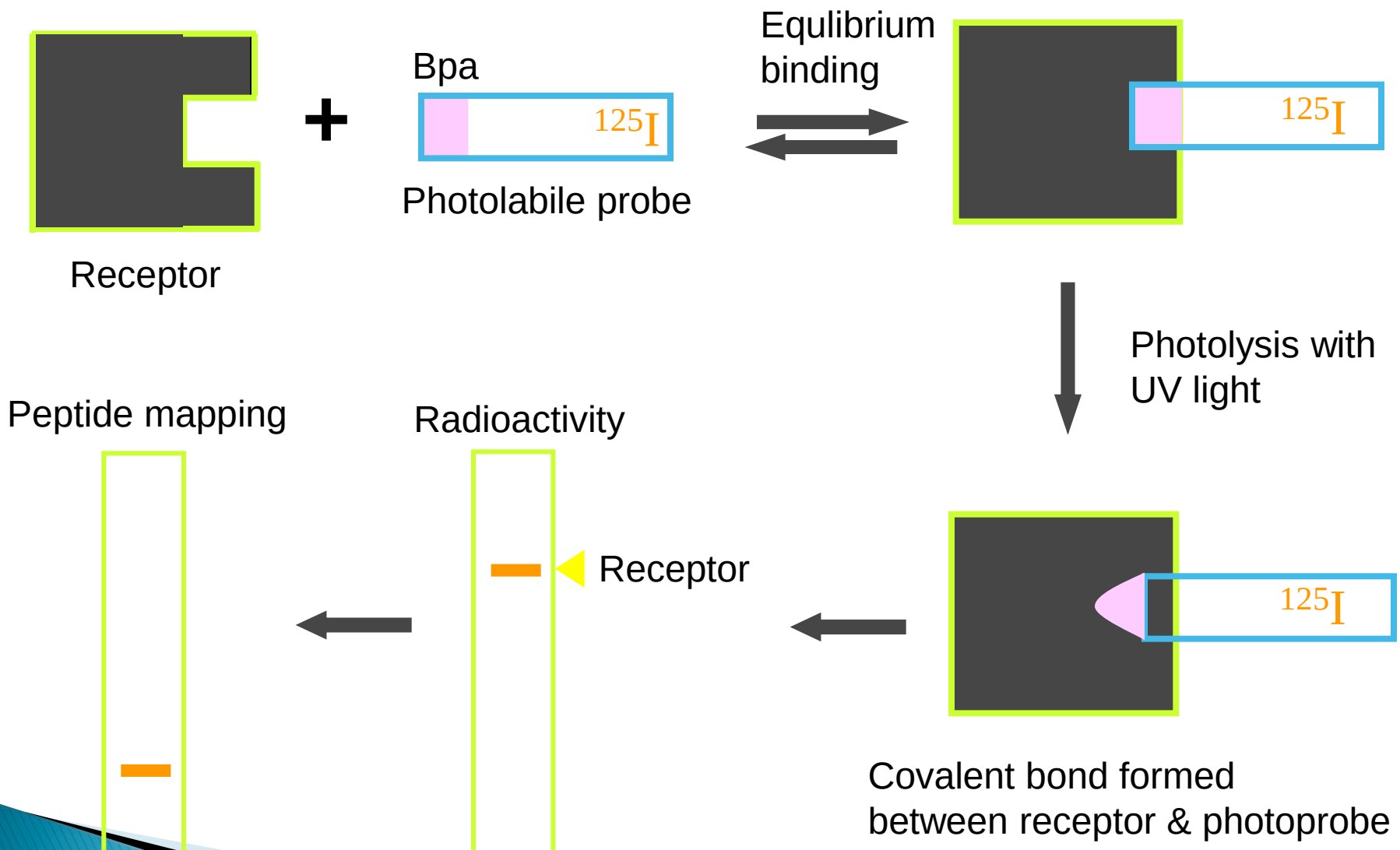


Doyle, 2007

Photoaffinity labeling

- Can probe spatial residue-residue approximations between the intact receptor and the docked ligand
- Complements best existing structural information derived from mutagenesis studies
- Provides constraints for establishment and refinement of molecular models of ligand-bound receptor

Intrinsic photoaffinity labeling



Photolabile GLP-1 probes

	7	10	15	20	25	30	35	
GLP-1(7-36 amide)	HAEGT**F**TSD**V**SS**Y*****L**EGQ**A**AKEFIAWLVK**G**R-NH_2							

N-terminal probes

[Bpa^{6}]GLP1	# (position 6)	R	R
[Bpa^{12}]GLP1	# (position 12)	R	R

Mid-region probes

[Bpa^{16}]GLP1	# (position 16)	R	R
[Bpa^{20}]GLP1	# (position 20)	R	R

C-terminal probes

[Bpa^{24}]GLP1	# (position 24)	R	R
[Bpa^{35}]GLP1		R	R #

= Benzoyl phenylalanine (Bpa)

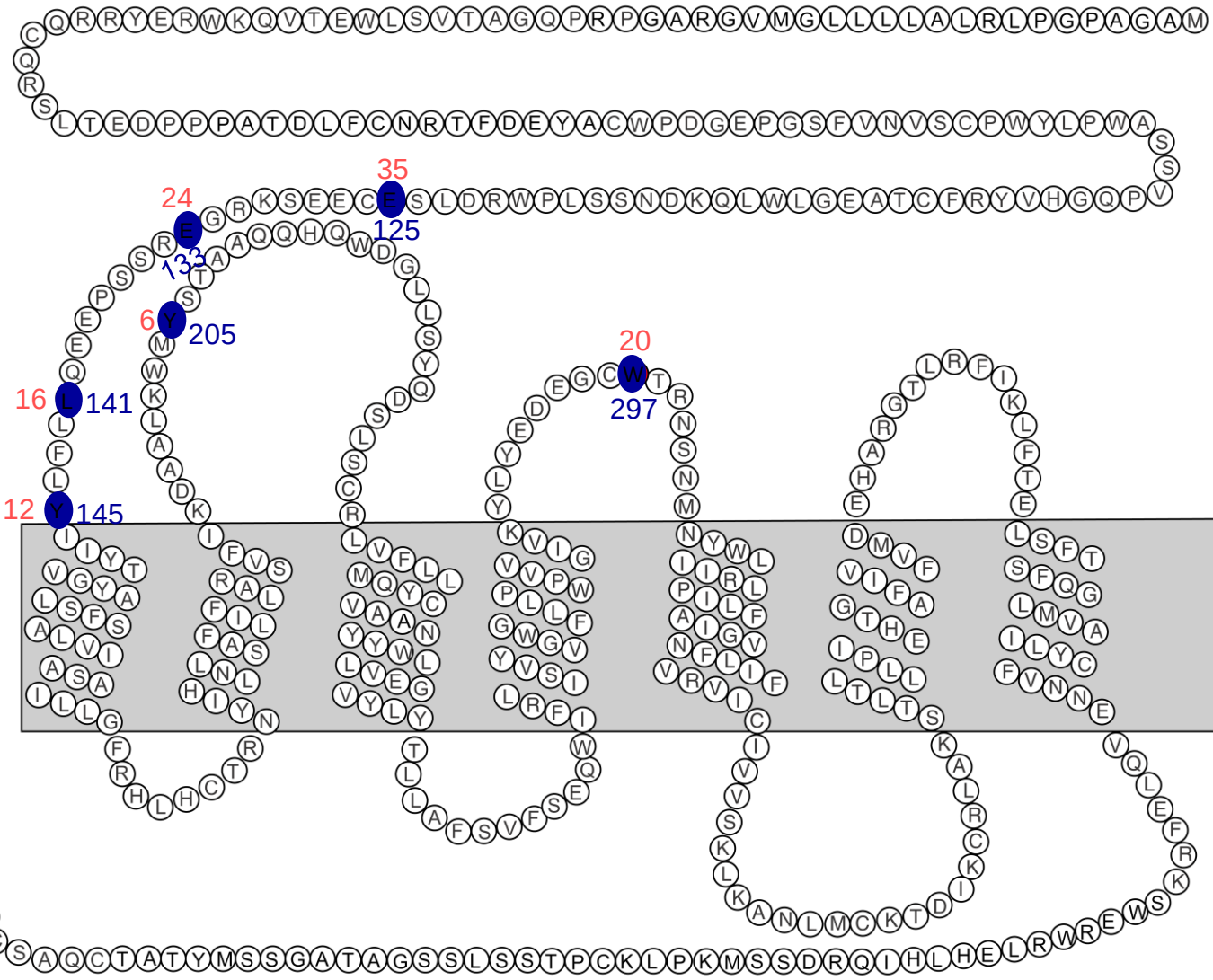
* = Site of radioiodination

MAYO CLINIC

Chen, et al, 2009 & 2010; Miller, et al., 2011

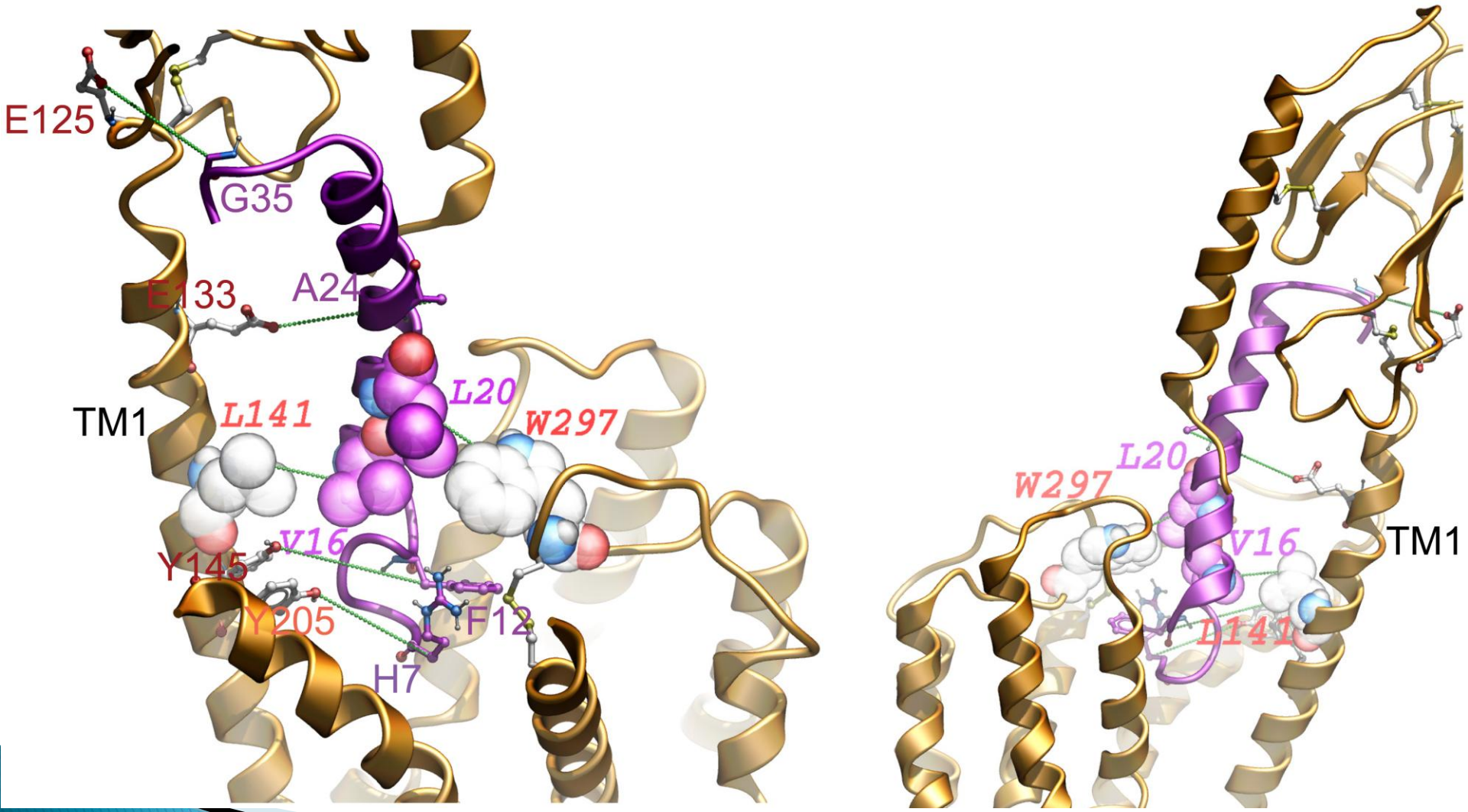
Constraints derived from our photoaffinity labeling study

GLP-1	GLP-1R
Bpa^{35}	E125
Bpa^{24}	E133
Bpa^{20}	W297
Bpa^{16}	L141
Bpa^{12}	Y145
Bpa^{6}	Y205



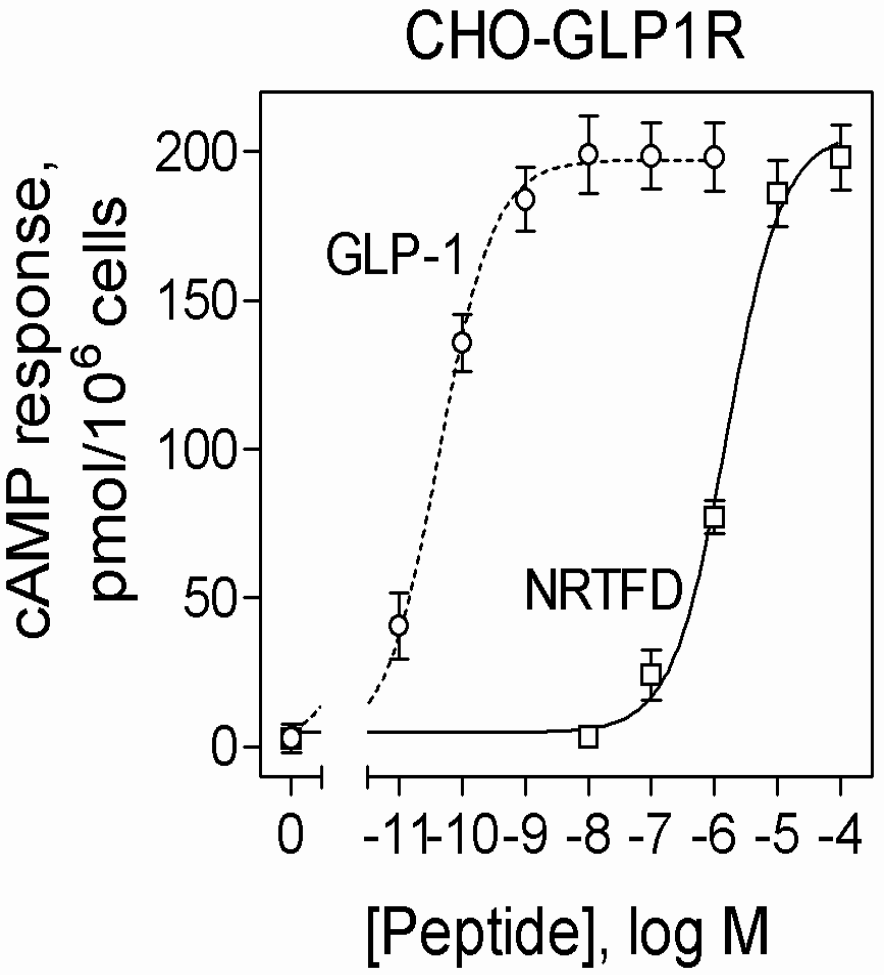
Chen, et al, 2009 & 2010; Miller, et al., 2011

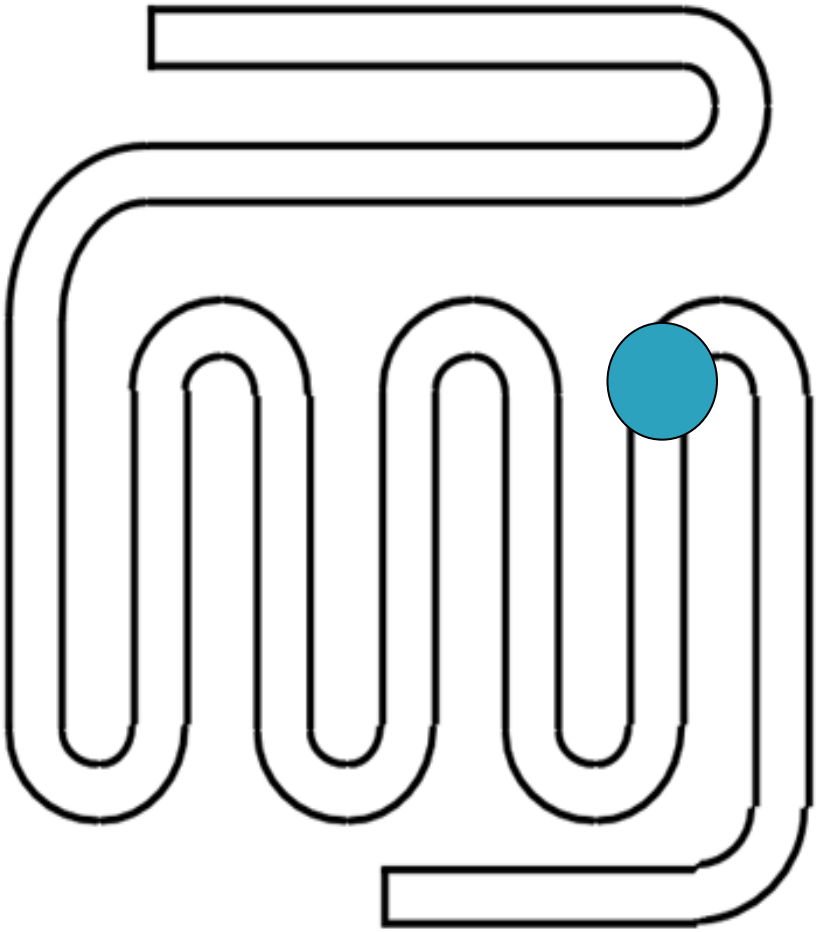
Molecular model of GLP-1 bound GLP-1 receptor



Miller, et al., 201

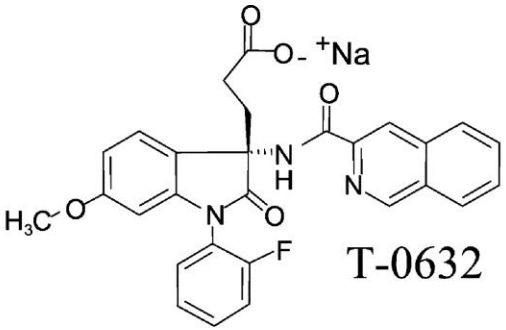
Endogenous agonist activity of the GLP-1 receptor peptide (NRTFD)

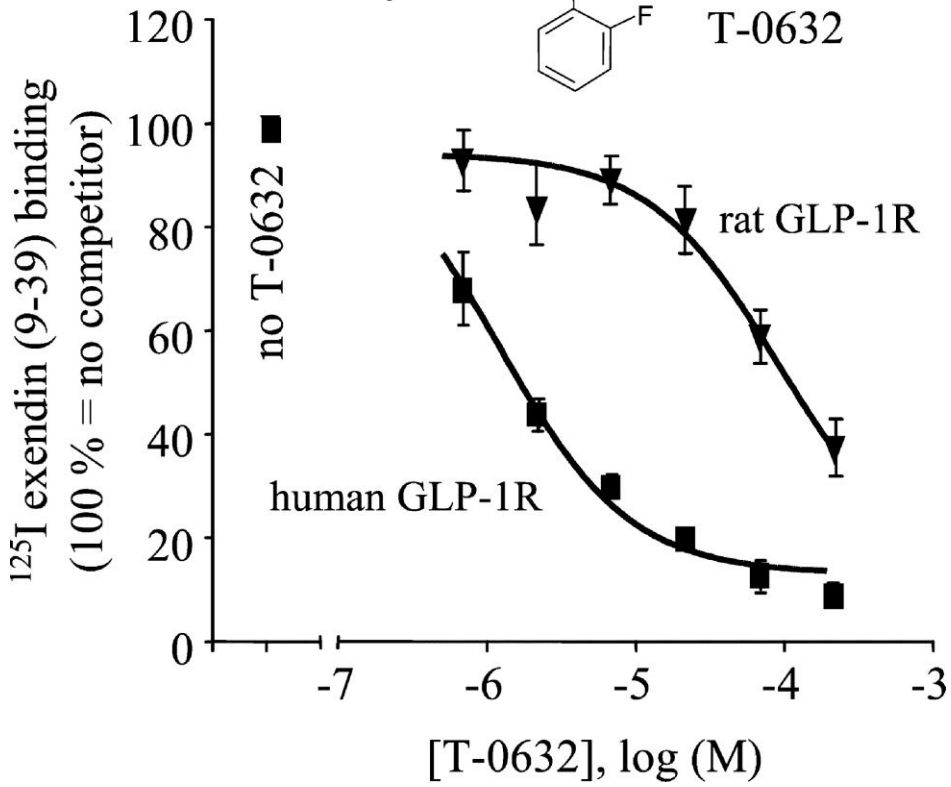


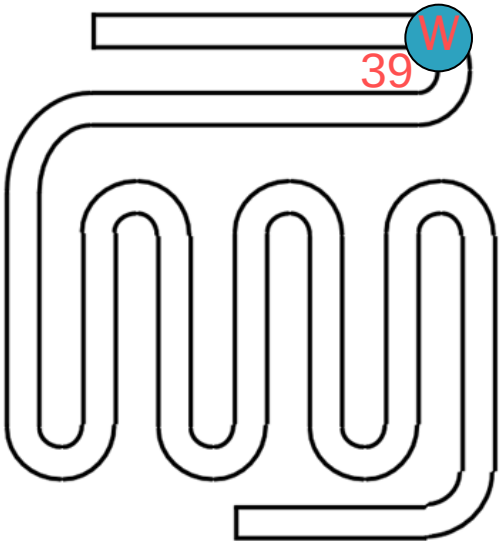


Dong, et al., 2008 & 2011

Small molecule GLP-1 receptor antagonist T-0632







Tibaduiza, et al., 2001

GLP-1 receptor small molecule agonists

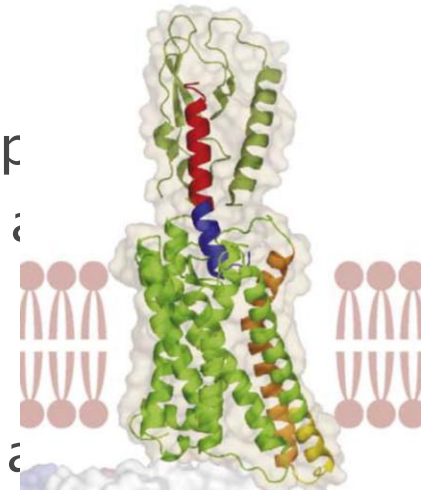
- Substituted cyclobutanes – BOC5 and S4P (Chen, et al., 2007)
  - Boc5 – full agonist; S4P – partial agonist
  - Both compete GLP-1 binding (Orthosteric site)
- Substituted quinoxalines – Compounds 1 and 2 (Knudsen, et al., 2007)
  - Cmpd 1 – partial agonist; Cmpd 2 – full agonist
  - Both do not compete GLP-1 binding (allosteric modulators)
- Pyrimidine-based compounds – Cmpd A and B (Sloop, et al. 2010)
  - Cmpd A – partial agonist; Cmpd B – full agonist
  - Cmpd B likely acts at TM regions
- Flavonoids – quercetin etc. (Wootten, et al. 2011)
- Molecular basis of actions of these molecules is not yet clear

Conclusions

- The GLP-1 receptor ECD folds into a unique structure that is functionally critical for ligand binding.

- Multiple residue-residue approximations have been established for GLP-1 and its intact receptor. While many fall within the ECD, the GLP-1 amino terminus and a mid-region residue interact with the receptor body (ECL1 and ECL2).

- The natural peptide ligand tethering two distinct recep domains could provide a mechanism to exert tension a thereby change receptor conformation.



- A growing number of small molecule drugs targeting a GLP-1 receptor have been discovered, but their mechanisms of action remain unclear and more potent drugs needs to be developed.

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