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# Gene Therapy of Diabetes & Obesity via siRNA-Based Silencing of the PTPN1 Gene (PTP1B) Protein

**JANUARY 2024**

CSE: PREV
OTCQB: PRVCF
FSE: 18H

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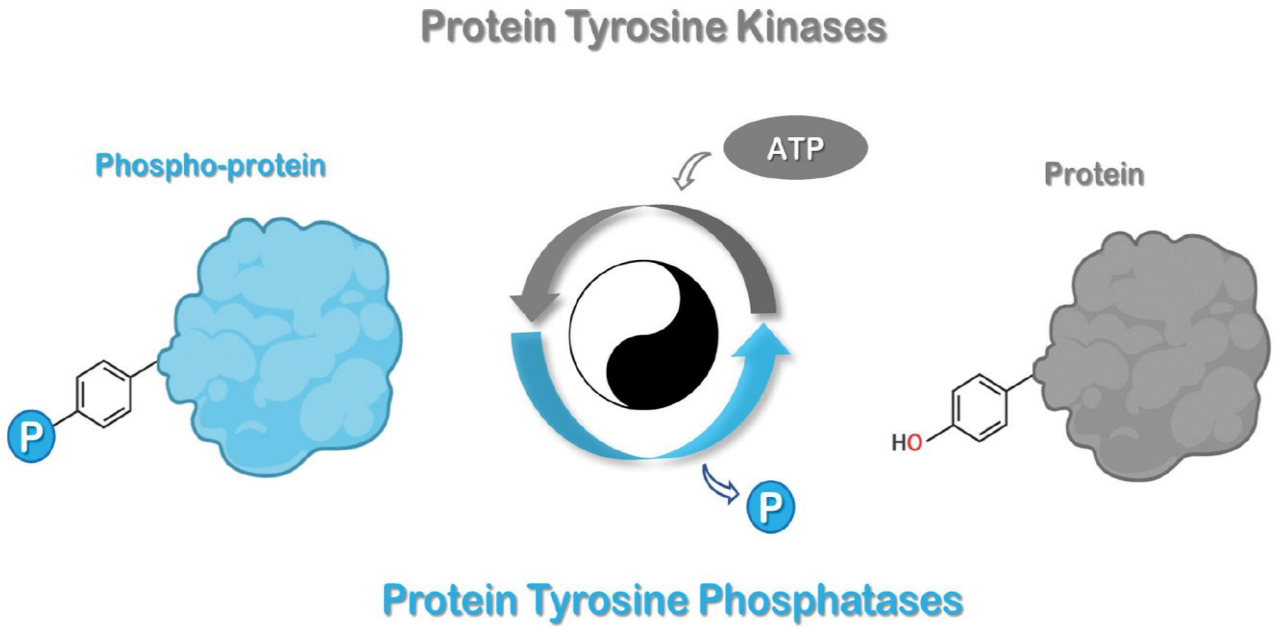
# Protein Tyrosine Phosphatases (PTPs)

PTPs are essential signalling enzymes, responsible for removing phosphate groups (on tyrosine) thereby reversing cellular signals initiated by growth factors, receptors and other tyrosine kinases.

Aberrant tyrosine phosphorylation, resulting from alteration of PTP expression, dysregulation, and mutation, has been linked to the aetiology of many human conditions including diabetes-&-obesity, cancer, autoimmune disorders and infectious diseases.

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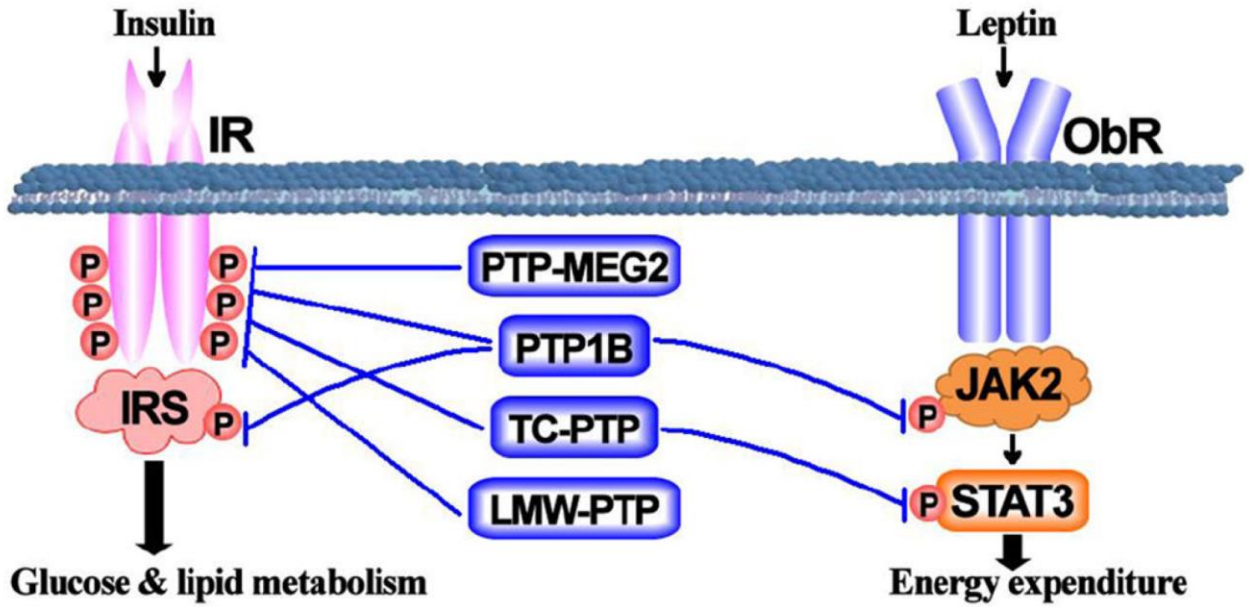
Adv Cancer Res. 2021 ; 152: 263–303. doi:10.1016/bs.acr.2021.06.001; Arch. Pharm. Res. (2021) 44:310–321
https://doi.org/10.1007/s12272-021-01315-9; Acc Chem Res. 2017 January 17; 50(1): 122–129. doi:10.1021/acs.accounts.6b00537

# PTP1B Causality in Diabetes & Obesity

Excessive PTP1B (protein, encoded by the PTPN1 gene) levels are responsible for dephosphorylating (and so deactivating) two KEY receptors that drive glucose metabolism, via the insulin receptor (IR) and leptin receptor activation, via the obesity receptor (ObR) primarily in liver, skeletal muscle and adipose tissue.

Disabling of the IR leads to insulin resistance i.e. insulin release triggers glucose bind to the GLUT receptor, but no intracellular migration of glucose. Concomitantly, fat metabolism is reduced.

Disabling the ObR leads to reduced energy expenditure from fat metabolism, leading to fat accumulation.

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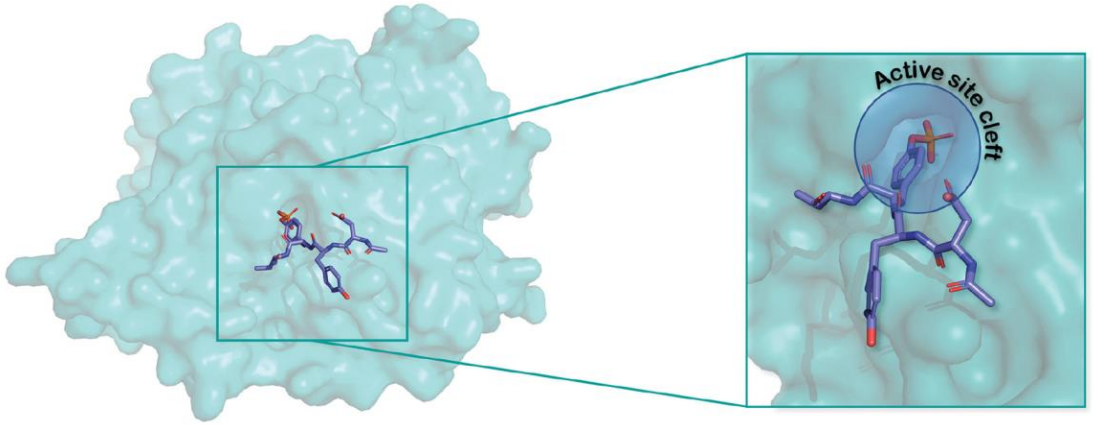
Adv Cancer Res. 2021 ; 152: 263–303. doi:10.1016/bs.acr.2021.06.001; Acc Chem Res. 2017 January 17; 50(1): 122–129. doi:10.1021/acs.accounts.6b00537

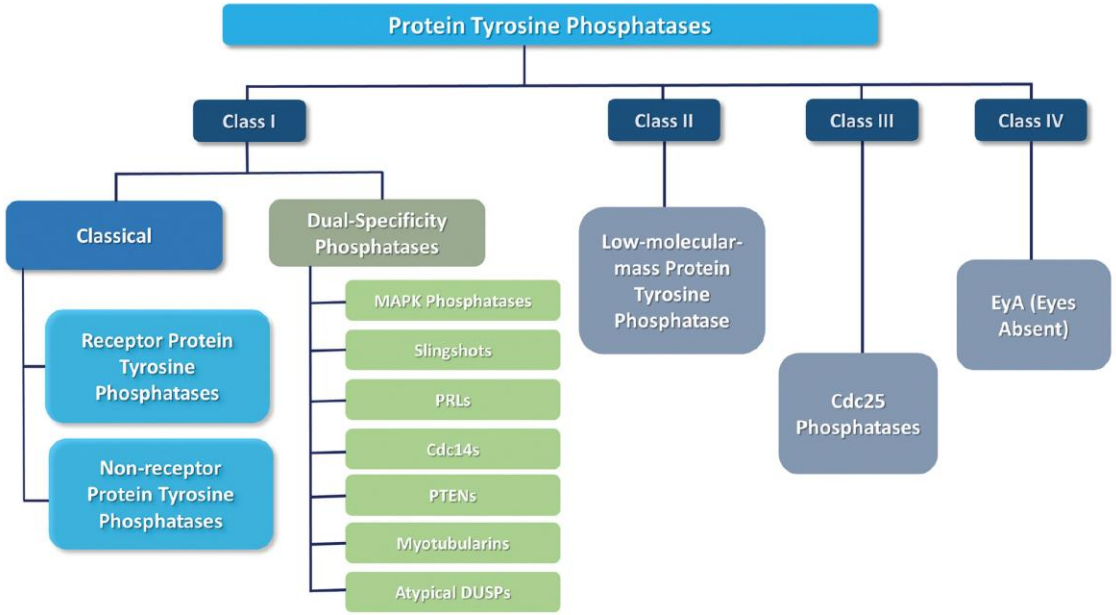
# Protein Tyrosine Phosphatases (PTPs) – drugging the undruggable!




PTPs have garnered significant attention over the past two decades as promising drug targets, however, successful translation of small molecules has remained elusive for a variety of key reasons:

## 01.

**A highly conserved active site (L, pTyr-binding pocket) has made it notoriously difficult to achieve inhibitor selectivity among the closely related super-family of PTPs (R, Class I-IV)**

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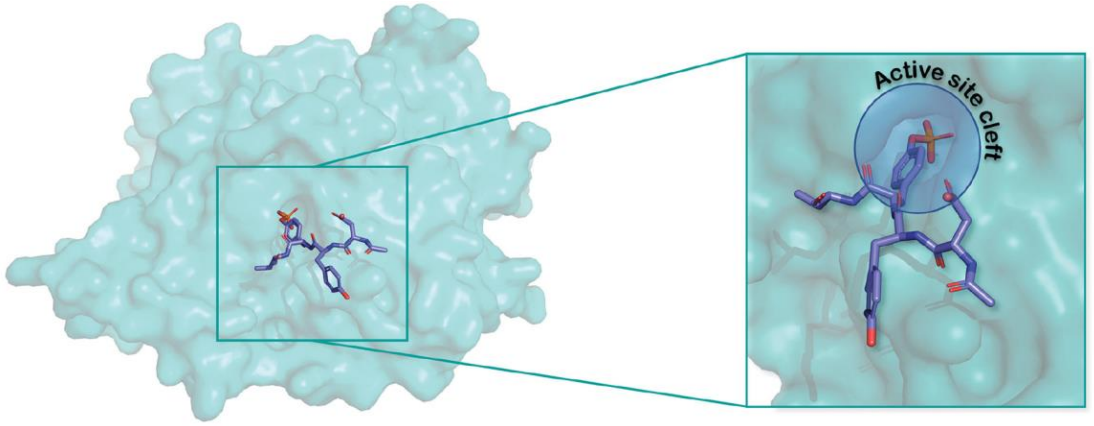
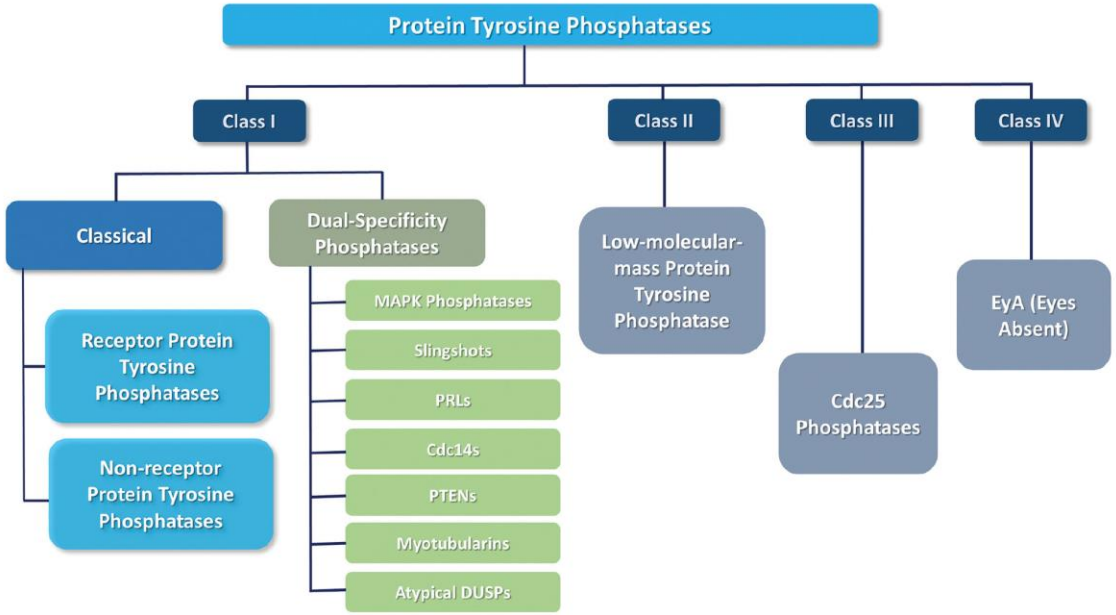



PTPs have garnered significant attention over the past two decades as promising drug targets, however, successful translation of small molecules has remained elusive for a variety of key reasons:

## 02.

**The positively-charged active site prefers negatively charged molecules, which lack specificity and cell permeability (akin to 'genes' which are also multiply negatively charged, and so require vectors!)**

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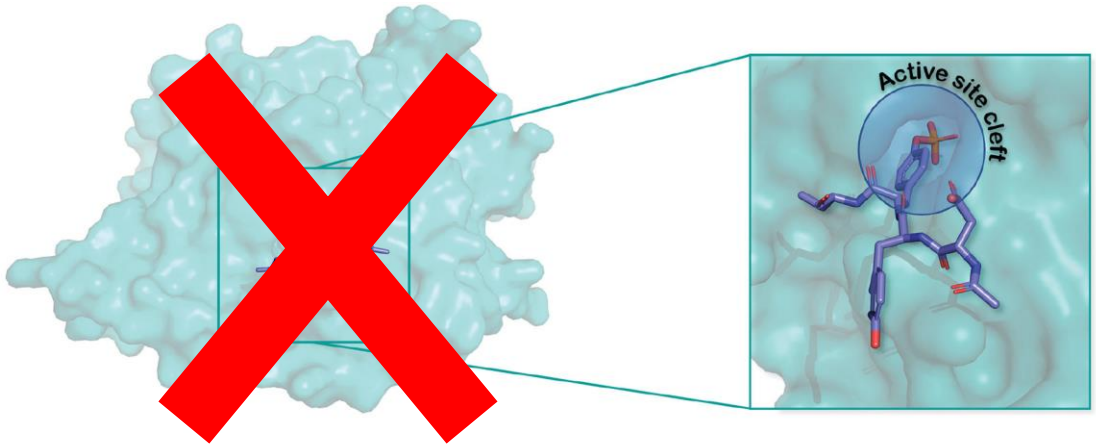
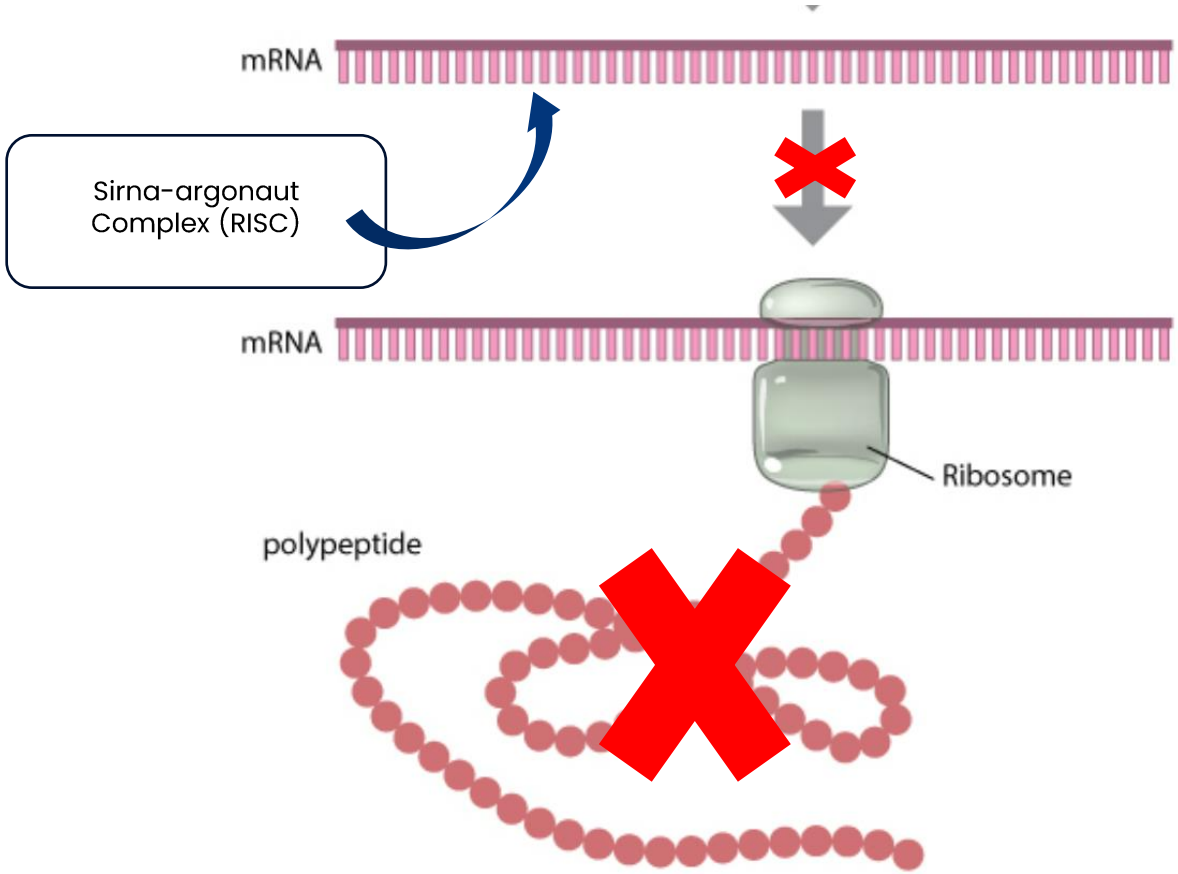
# Protein Tyrosine Phosphatases (PTPs) – drugging the undruggable!

Targeting the PTPN1 gene that ONLY encodes for the PTP1B protein – precise, specific…

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# PTPN1 Gene Targeting Strategy With Smart-sirna's

PTPN1 gene comprises 10 exons, each are potential targets for siRNA:


Successfully engineered selective, potent siRNA's independently targeting multiple exons of PTPN1

siRNA's against both mouse and human variants of distinct exons were engineered in parallel, paving the way for PoC preclinical and clinical studies

siRNA sequences were engineered to be biostable ('Smart-siRNAs'), and novel w.r.t the prior art/published sequences

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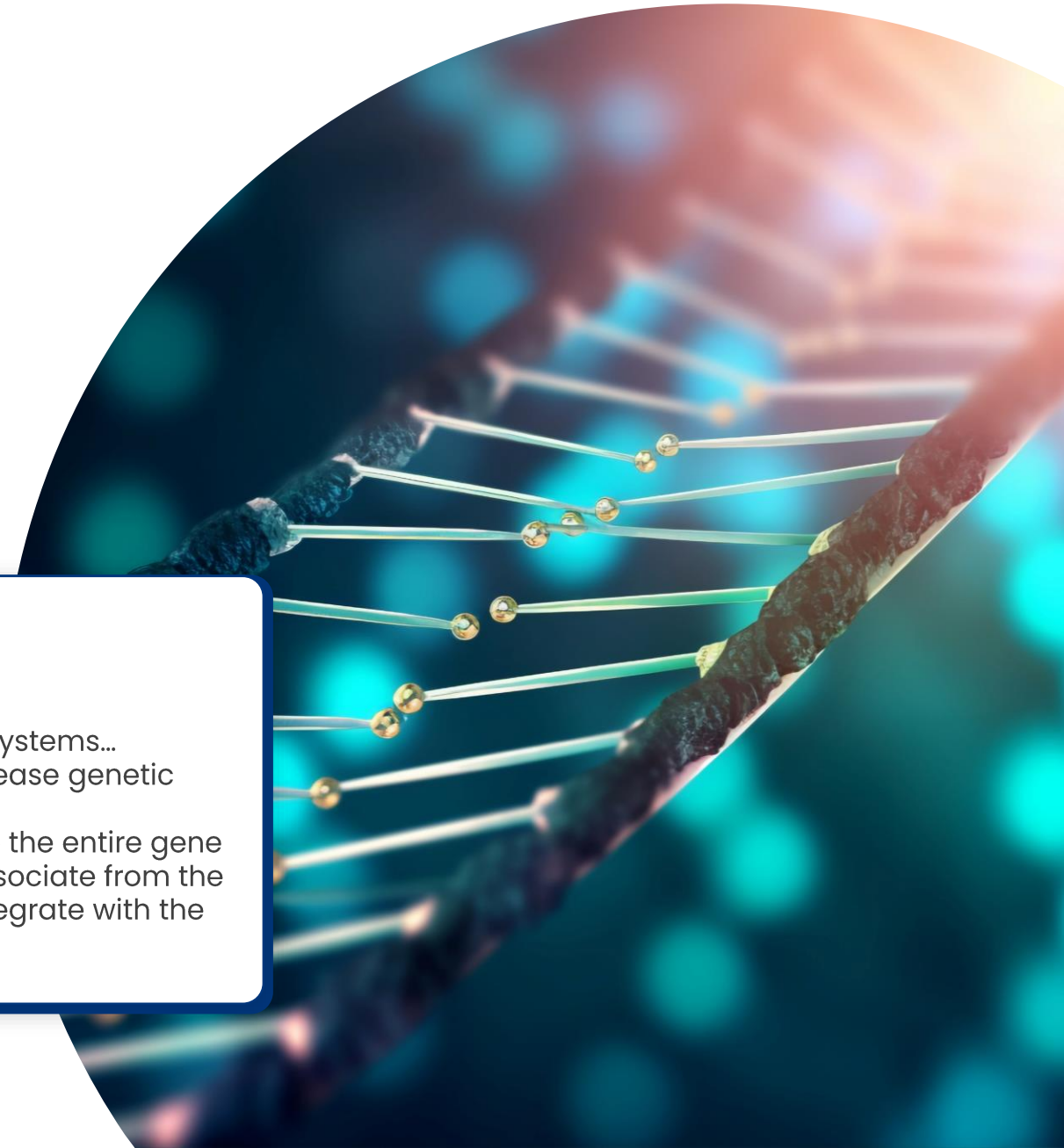
# Non-viral Vectors - Bioresponsive Lnps (BInp)

Library of non-viral, self-assembling bio-inspired bLNPs that employ naturally-derived lipids and amino acids

Discrete design, readily tailored to gene construct of interest (10's bases thru 1k's, 100k's bases) synthesised using robust well-established chemistries in high yield and scalable



Possess a unique bioresponsive 'gene-releasing' mechanism, US Patent 11,566,044 – granted 31-Mar-23

- NOT to be confused with fusogenic lipids/endosomal escape systems…
- Systems possess endosomal escape features AND actively release genetic cargo from cationic carrier lipids
- This latter step is largely dismissed in LNP design, yet critical so the entire gene cargo load (siRNA, mRNA, pDNA etc.) can comprehensively dissociate from the cationic lipids, re-establish their natural conformation, and integrate with the cellular machinery (e.g. RNAi)

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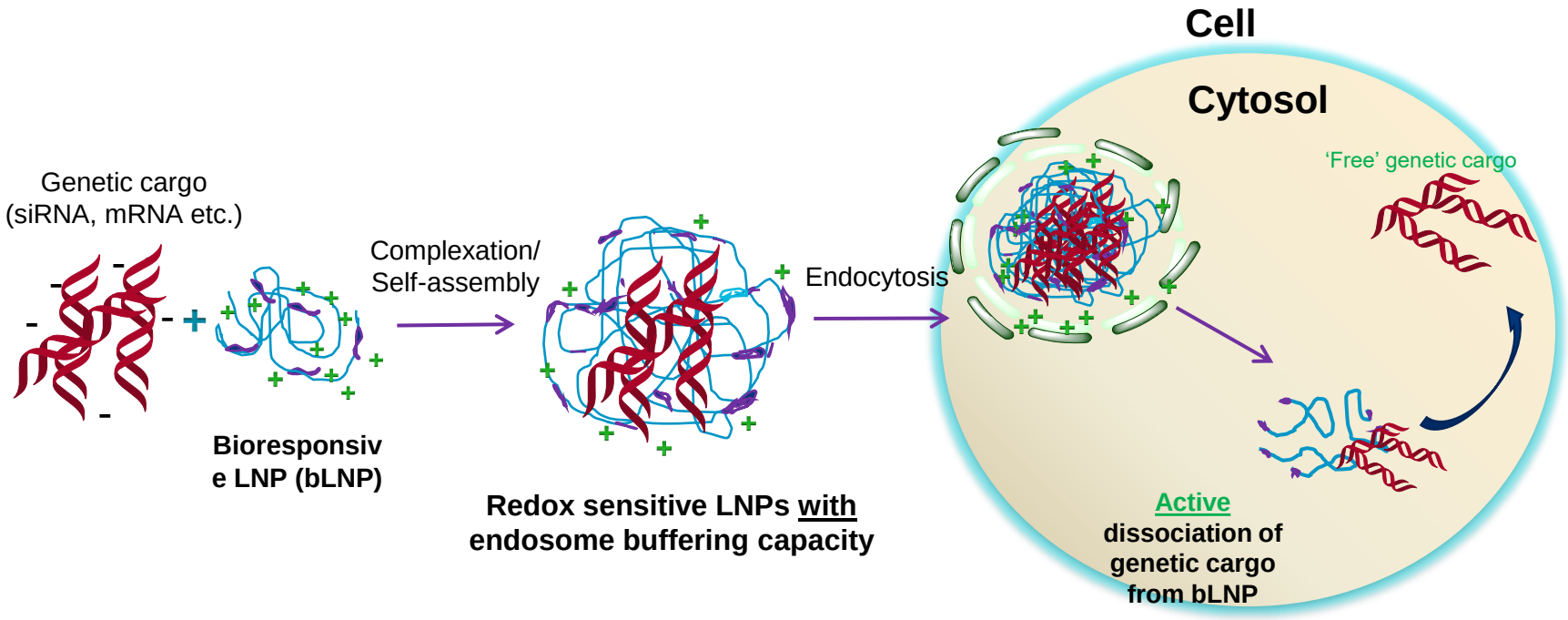
# Bioresponsive Self-assembling Lnps




Circumvents endo-lysosomal degradation of bLNP-genetic cargo

- Improved gene delivery and release leading to enhanced efficacy
- Potential to vastly lower siRNA doses…
- Linker highly stable to broad range of chemistries…

**Comprehensive intracellular gene release** → ↑↑↑ **Efficacy**

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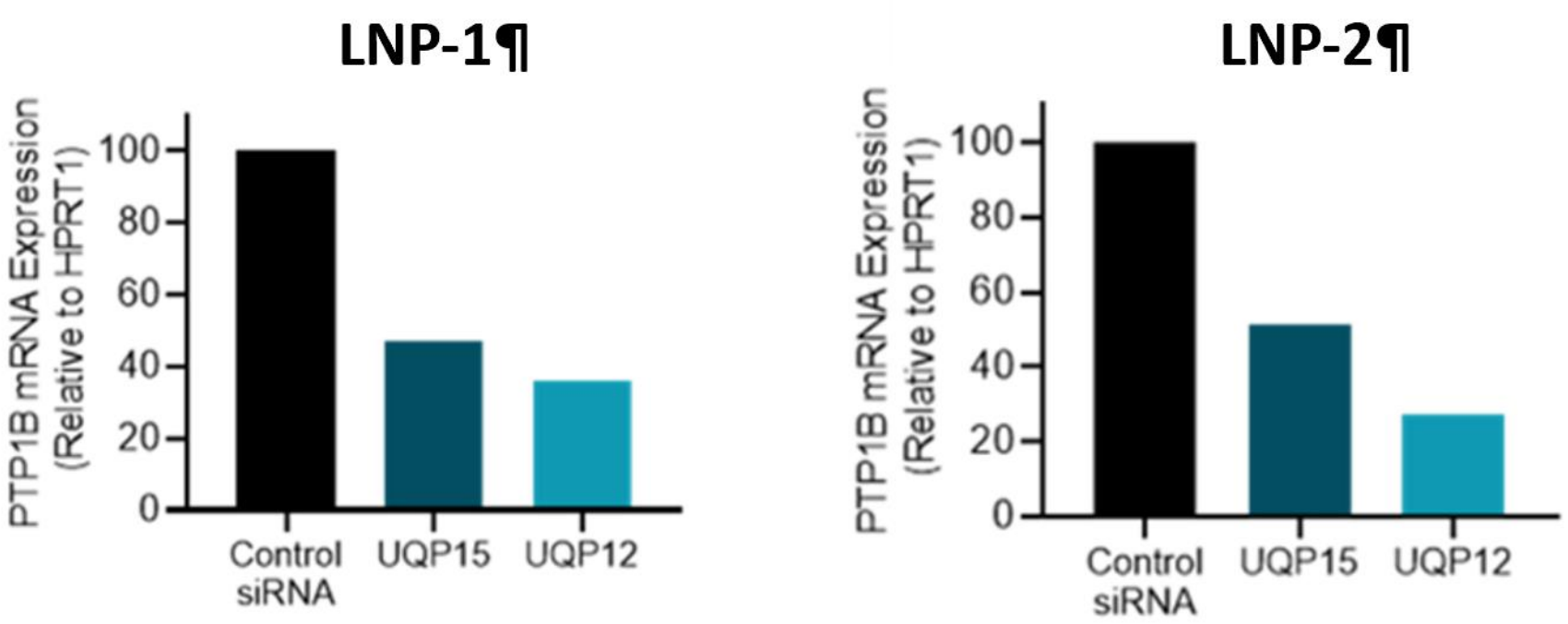
# Confirmed Potent Gene Silencing With Bioresponsive Lnps

LNPs possessing the unique bioresponsive 'gene-releasing' linker (US Patent 11,566,044 – granted 31/Mar/23)

- siRNA's that target multiple different exons were engineered
- Examples of select, Smart-siRNA's (UQP15 & UQP12) and their gene silencing ability (>50%) with two bioresponsive-LNPs are shown below:

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# GLP-1 (Glucagon Like Peptide-1) Agonists

GLP-1 lowers blood glucose by stimulating insulin secretion and production, and suppressing glucagon secretion in a glucose-dependent manner.

Ozempic (semaglutide) is a glucagon-like peptide 1 (GLP-1) receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. Predecessors include exenatide and liraglutide.

Also, GLP-1 decelerates gastric emptying, slows digestion, and induces satiety hormones acting in the brain, with issues emerging:

## Ozempic Label Updated to Include Blocked Intestines as Potential Side Effect


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Healthcare & Pharmaceuticals | Product Liability | Regulatory Oversight | Regulatory | Health

## Wegovy, other weight-loss drugs scrutinized over reports of suicidal thoughts

By **Robin Respaut** and **Chad Terhune**

October 13, 2023 4:15 AM GMT+10 · Updated a month ago

Aa

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# Precision Medicine-Based Approach to Diabetes & Obesity

- 'Smart-siRNAs' are biochemically stable, possess selective, potent PTPN1 gene-silencing properties (confirmed protein-level silencing).
- Patented bioresponsive linker provides a platform path to self-assembled bLNPs, providing for safe (non-immunogenic), effective (endosomal escape-carrier dissociation), scalable platform for ANY genetic cargo.
- **Smart-siRNA-bLNP complexes possess highly effective gene and protein silencing (c.f. standard LNPs), confirmed both in vitro and ex vivo liver tissue**
- PoC preclinical studies in diabetic & obese mice are planned next…
- The platform-based, precision medicine approach opens the door to also evaluating PTP1B protein silencing in diseases beyond diabetes & obesity i.e. cancer, autoimmune disorders and infectious diseases.

| Tumor Promoter | | |
|---|---|---|
| **PTP** | **Cancer** | **Alteration** |
| PTPα | CRC, Head and Neck | Overexpression |
| | Gastric | Overexpression |
| PTPβ, PTPζ | Glioma, melanoma | Overexpression |
| | Gastric | Overexpression |
| LAR | Thyroid, Breast | Overexpression |
| PTPγ | Glioma, gastric, lymphoma | Overexpression |
| SAP1 | Gastrointestinal, CRC | Overexpression |
| PTP1B | Breast, Ovarian | Overexpression |
| | Gastric, pancreatic | Amplification |
| | Prostate | Overexpression |
| PTPH1 | Gastric, Oesophageal | Overexpression |
| SHP1 | Ovarian | Overexpression |
| LCPTP | Leukemia | Amplification |
| SHP2 | Leukemia | Mutation |
| PTPD1 | CRC | Mutation |

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# Thank You!

CHEMICAL REVIEWS

Review

pubs.acs.org/CR

**Type 2 Diabetes Mellitus: Limitations of Conventional Therapies and Intervention with Nucleic Acid-Based Therapeutics**

Ganesh R. Kokil,[†] Rakesh N. Veedu,[*,‡,§,∥] Grant A. Ramm,[⊥,#] Johannes B. Prins,[▽] and Harendra S. Parekh[*,†]

Research Article

Journal of PeptideScience

Received: 12 October 2010 Revised: 24 November 2010 Accepted: 1 December 2010 Published online in Wiley Online Library:

(wileyonlinelibrary.com) DOI 10.1002/psc.1347

**Low-generation asymmetric dendrimers exhibit minimal toxicity and effectively complex DNA**

Neha Shah,[a,b] Raymond J. Steptoe[b*] and Harendra S. Parekh[a*]

*J. Phys. Chem. B* **2010,** *114,* 9231–9237 **9231**

**Structure and Dynamics of Multiple Cationic Vectors−siRNA Complexation by All-Atomic Molecular Dynamics Simulations**

Defang Ouyang,[†,‡] Hong Zhang,[‡] Harendra S. Parekh,[*,†] and Sean C. Smith[*,‡]

*School of Pharmacy and Centre for Computational Molecular Science, Australian Institute of Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD 4072, Australia*

*Received: December 17, 2009; Revised Manuscript Received: June 1, 2010*

ELSEVIER

Advanced Drug Delivery Reviews

Available online 8 January 2015

In Press, Corrected Proof — Note to users

**Are caveolae a cellular entry route for non-viral therapeutic delivery systems?** ☆

Prarthana V. Rewatkar[a], Robert G. Parton[b], Harendra S. Parekh[a], Marie-Odile Parat[a]

Journal of PeptideScience

The official Journal of the European Peptide Society

EPS

Research Article | Full Access

**Low-generation asymmetric dendrimers exhibit minimal toxicity and effectively complex DNA**

Neha Shah, Raymond J. Steptoe, Harendra S. Parekh

First published: 24 February 2011 | https://doi.org/10.1002/psc.1347 | Citations: 46

Pharm Res (2014) 31:3150–3160

DOI 10.1007/s11095-014-1408-1

RESEARCH ARTICLE

**Asymmetric Peptide Dendrimers are Effective Linkers for Antibody-Mediated Delivery of Diverse Payloads to B Cells in Vitro and in Vivo**

Neha D. Shah • Harendra S. Parekh • Raymond J. Steptoe

SCIENTIFIC REPORTS

OPEN

**Self-assembling asymmetric peptide-dendrimer micelles – a platform for effective and versatile *in vitro* nucleic acid delivery**

Received: 29 August 2017
Accepted: 12 February 2018
Published online: 19 March 2018

Ganesh R. Kokil[1], Rakesh N. Veedu[2,3,4], Bao Tri Le[2,3], Grant A. Ramm[5,6] & Harendra S. Parekh[1]

ADVANCED THEORY AND SIMULATIONS

Full Paper | Full Access

**Cell Membrane Penetration without Pore Formation: Chameleonic Properties of Dendrimers in Response to Hydrophobic and Hydrophilic Environments**

Sergio de Luca, Prasenjit Seal, Harendra S. Parekh, Karnaker R. Tupally, Sean C. Smith

First published: 03 June 2020 | https://doi.org/10.1002/adts.201900152

ACS Biomaterials SCIENCE & ENGINEERING

Article

pubs.acs.org/journal/abseba

**Express in Vitro Plasmid Transfection Achieved with 16[+] Asymmetric Peptide Dendrimers**

Prarthana V. Rewatkar,[†] David P. Sester,[‡] Harendra S. Parekh,[*,†] and Marie-Odile Parat[*,†]

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Supporting Information

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