From Type-2 to None: Imagining a world without Diabetes

RESULTS PRESENTATION BY

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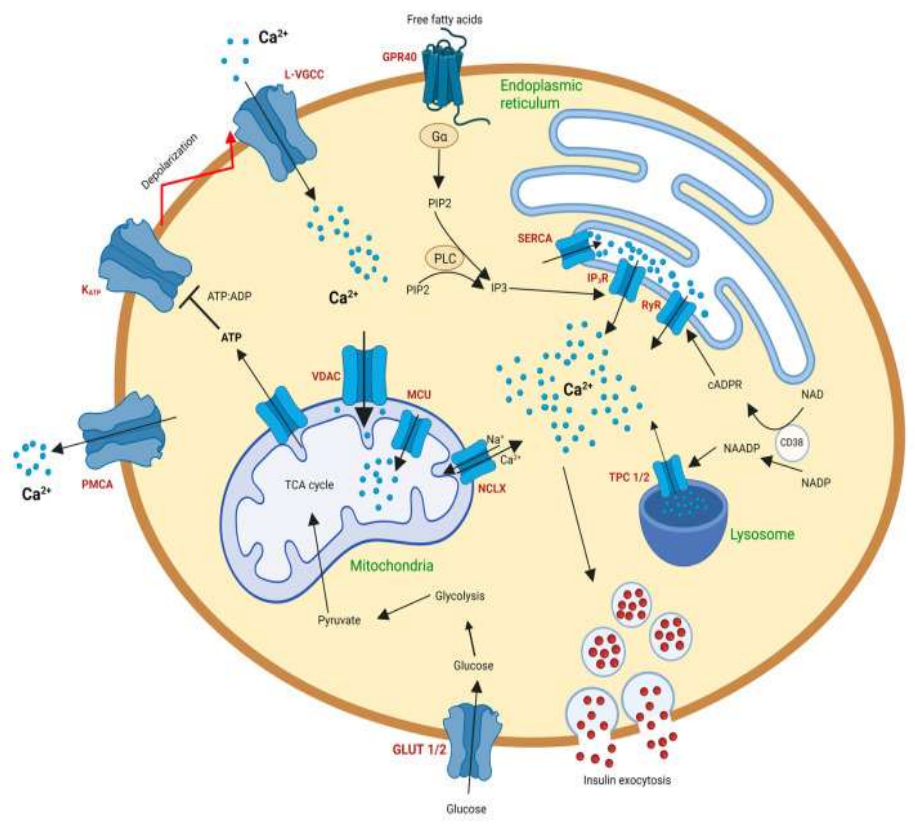
Brief overview about the disease and challenges

- Type 2 Diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance and beta-cell dysfunction, leading to hyperglycemia.
- Targeting beta-cell proliferation to increase the number of insulin-producing cells and enhancing insulin sensitivity to improve glucose uptake.
- First approach: DYRK1A (dual-specificity tyrosine-phosphorylation-regulated kinase 1A) inhibitors; DYRK1A inhibitors have shown significant toxicity to the liver, limiting their therapeutic use.
- Second approach: Gene Therapy; T2D is not caused by a single genetic mutation but results from a complex interplay of genetic, environmental, and lifestyle factors. This complexity makes it difficult to identify a single gene target for therapy.

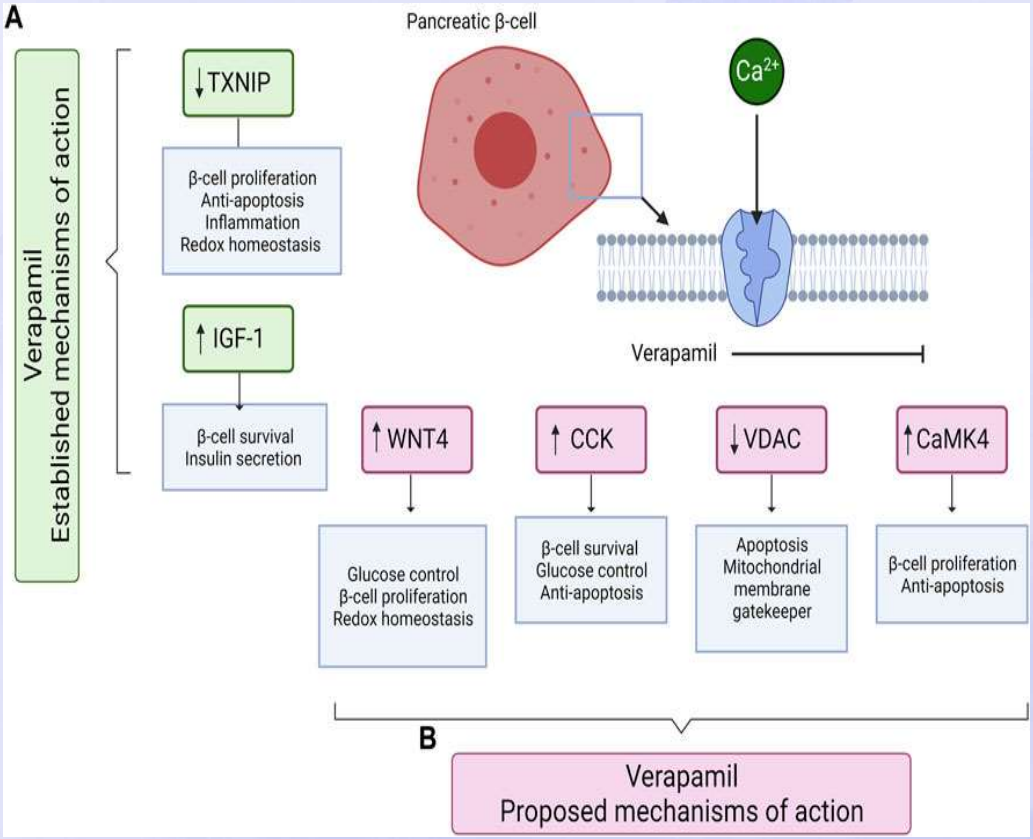
Selected Approach

- Drug repurposing offers a promising avenue for finding new treatments for Type 2 Diabetes (T2D) by leveraging existing medications that were originally developed for other conditions.
- Drug selected: **Verapamil,** a calcium channel blocker that is primarily used to treat high blood pressure, angina, and certain heart rhythm disorders.
- Recent studies have shown that modulating Ca2+ influx in the context of beta cells, can potentially improve insulin secretion and help manage blood glucose levels.



Targeting Type 2 Diabetes with Verapamil

- Verapamil has been shown to inhibit the expression of thioredoxin-interacting protein (TXNIP) which resulted in decreased β-cell apoptosis and enhanced endogenous insulin levels.
- Previous studies have focused on verapamil as a monotherapy or in combination with trandolapril.
- Conjugate verapamil with exendin. Dual mechanism of action- verapamil's potential to protect β-cells and improve insulin levels, and Exendin's ability to enhance insulin secretion and control glucagon levels.

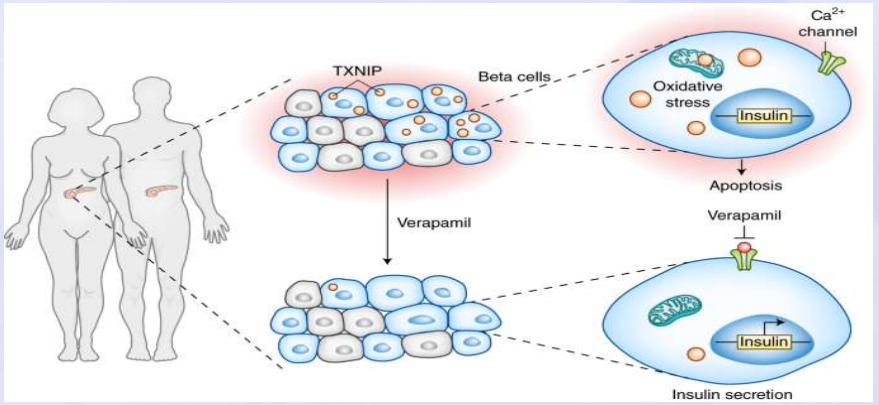


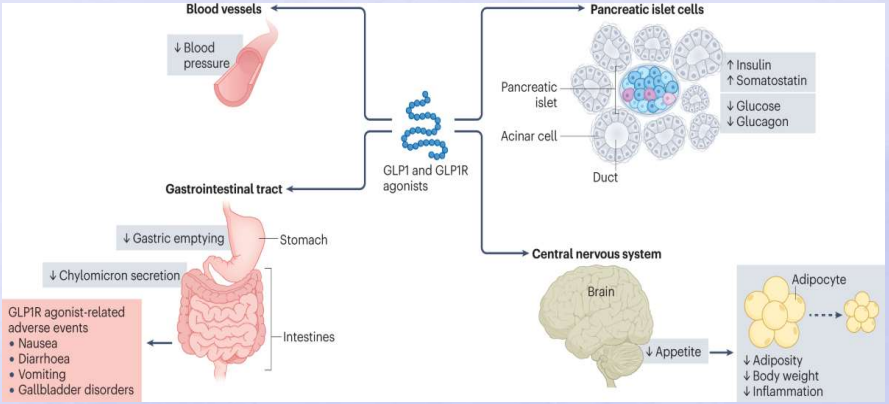
Reason for selecting verapamil-exendin combination

- By conjugating verapamil with peptides like exendin-4 that binds specifically to GLP-1 receptors, which are highly expressed on pancreatic beta-cells, can enhance its specificity for the pancreas.
- Dual purpose: This conjugation act as both delivery system for verapamil and help in improving the glycemic control.
- Targeting insulin resistance early in the disease progression is a critical strategy for treatment and potentially reversing the condition.
- By addressing both the preservation of β-cell function and the enhancement of insulin sensitivity and secretion, the Verapamil-Exendin conjugate offers a comprehensive strategy for targeting insulin resistance early in T2D.

Targets and Purposed Treatments

- **Molecular Targets:**
- TXNIP in β-cells: Verapamil inhibits thioredoxin-interacting protein (TXNIP), which is implicated in β-cell apoptosis.
- GLP-1 Receptor: Exendin acts as a GLP-1 receptor agonist, enhancing insulin secretion in a glucose-dependent manner and improving insulin sensitivity in peripheral tissues.
- The combination of Verapamil and Exendin, will be administered either **orally** or through **injection.**

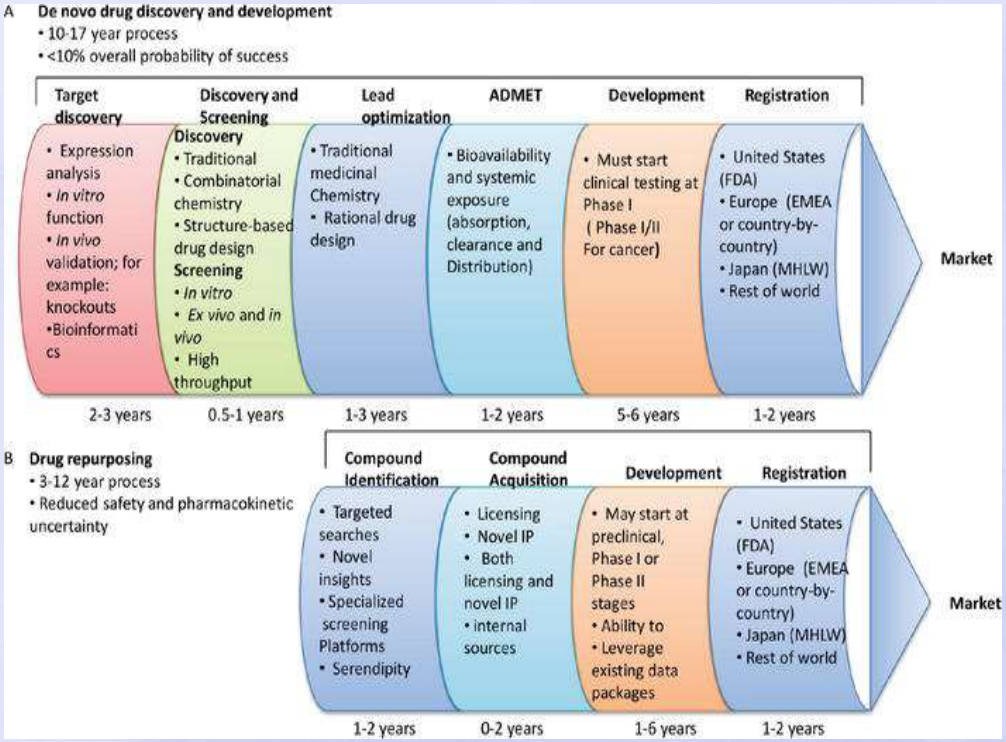




Drug discovery Process

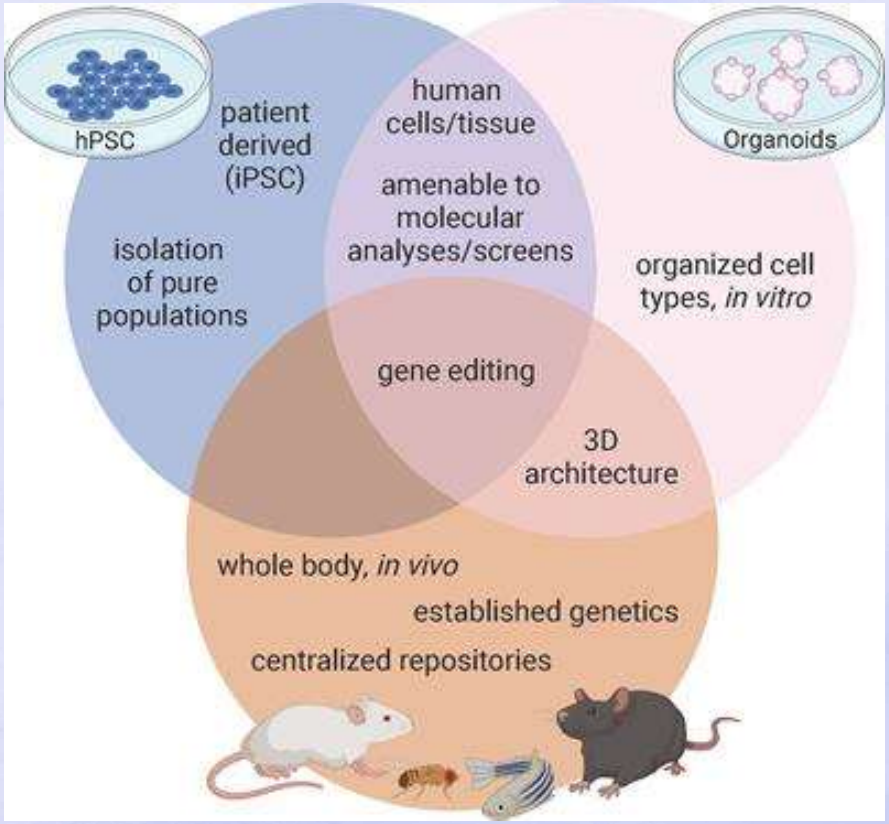
- This process starts with the identification of candidate drug that have already undergone significant development, including safety and pharmacokinetic profiling, for other indications.

1. **Preclinical Validation**
2. **ADMET and Toxicology Studies**
3. **Clinical Trials and FDA Approval**



Pre-clinical validation

- **Animal models:**
- **db/db mice:** These mice carry a mutation in the leptin receptor gene, leading to obesity, insulin resistance, and eventually β-cell dysfunction, closely mimicking the progression of human T2D.
- The **Goto-Kakizaki (GK) rat** is a nonobese, nonhypertensive model of type 2 diabetes, which, like humans, shares a susceptibility locus on chromosome 10. It develops adult onset type 2 diabetes early in life.
- Utilize pancreatic beta-cell **organoids** to study the drug's effects in a human-relevant system.



Pre-clinical validation: Biochemical assays

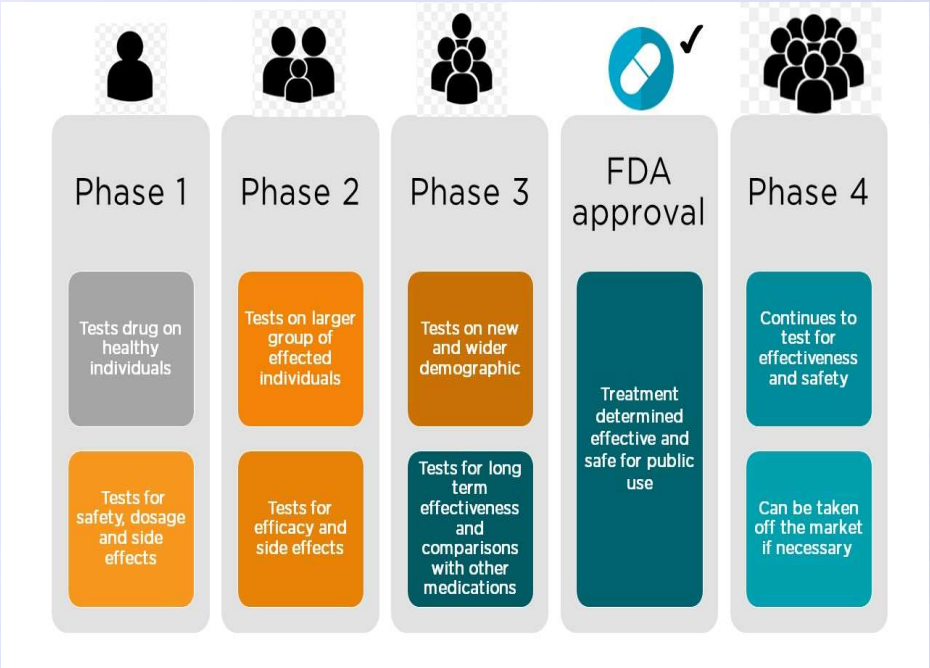
- Conduct assays to evaluate the effects of the Verapamil-exendin conjugate on insulin secretion, beta-cell viability, and GLP-1 receptor activation.
- Animal studies utilize diabetic rodent models to assess glycemic control, lipid profiles, and organ histology. Organoid cultures mimic pancreatic islet function and response to treatment.
- Throughout these steps, various bioinformatics tools and techniques can be employed to analyze data, including:
- **Gene Expression Analysis**: Tools like DESeq2 or edgeR can be used for analyzing RNA-seq data to identify differentially expressed genes.
- **Pathway Analysis**: Tools like clusterProfiler can help in understanding the pathways that are significantly affected by the drug treatment.
- **Statistical Analysis**: R and Python libraries (e.g., pandas, numpy, scipy) can be used for statistical analysis and data visualization.

Pre-clinical validation: ADMET and Toxicology Studies

- Comprehensive ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies will be conducted to evaluate Verapamil's pharmacokinetics and safety profile in the context of T2D. These studies will include assessments of potential drug-drug interactions and long-term toxicity evaluations.
- Safety pharmacology studies examine cardiovascular, hepatic, renal, and hematological parameters.
- Tools used for these studies:
- NONMEM (Nonlinear Mixed Effects Modeling): For pharmacokinetic/pharmacodynamic (PK/PD) modeling, widely used in drug development.
- Simcyp Simulator or GastroPlus: For simulating and predicting the absorption, distribution, metabolism, and excretion (ADME) of drugs in humans and animals.
- ToxRTool: For assessing the reliability of toxicology data.
- ADMET Predictor: For predicting the absorption, distribution, metabolism, excretion, and toxicity of chemicals.

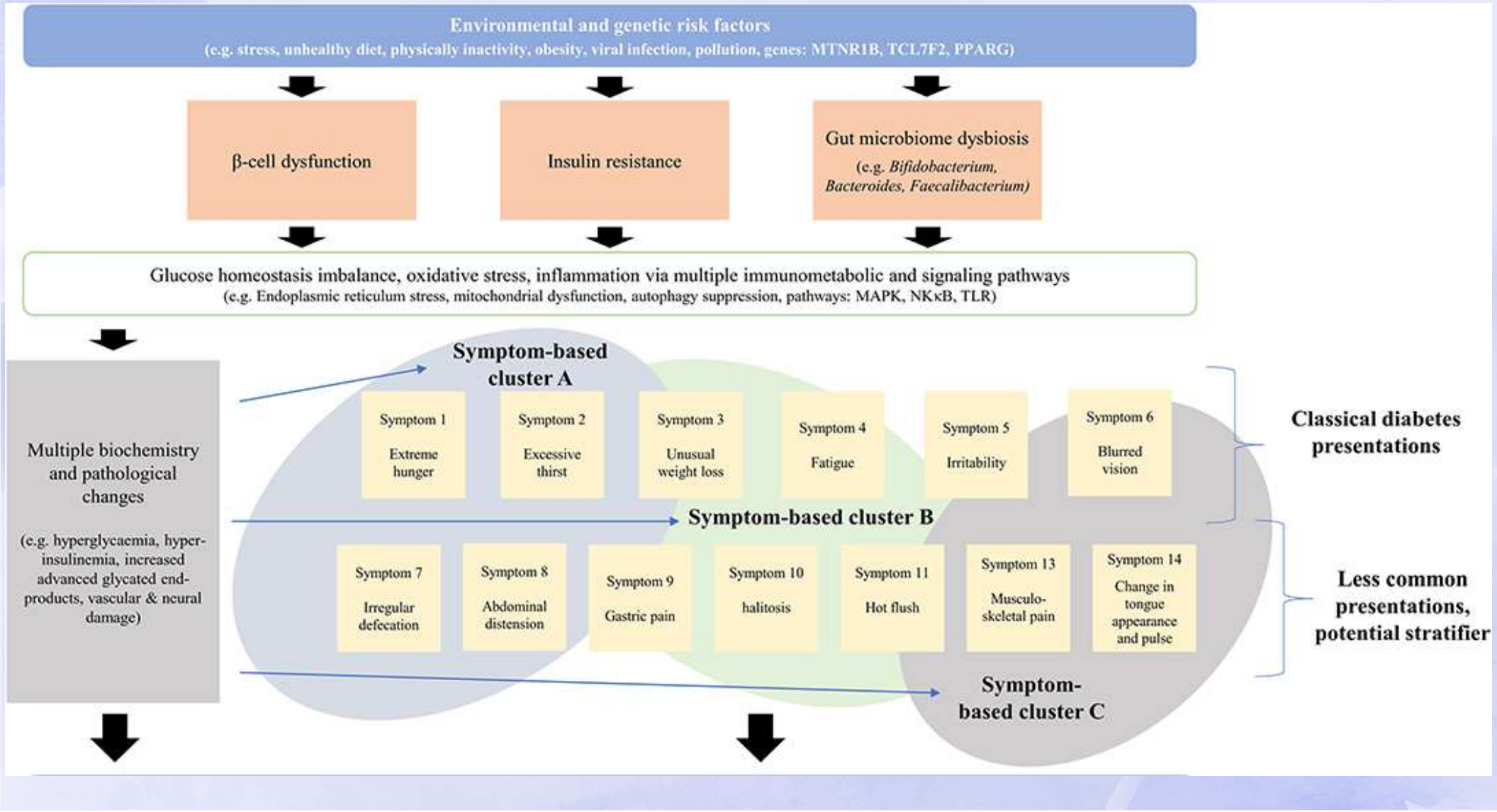
Phases of FDA drug approval

- **Phase I**: Safety and Pharmacokinetics: Focus on drug interaction with new indication.
- **Phase II**: Efficacy and Dose-Finding: Evaluate initial efficacy signals and determine effective dosing
- **Phase III**: Confirmatory Trials: Confirm efficacy and safety in larger population and assess long-term outcomes
- **Phase IV**: Post-Marketing Surveillance: Monitor real-world safety and effectiveness and gather data on rare adverse events



Patient Population Selection

- Inclusion Criteria: Adults diagnosed with T2D, particularly those with evidence of insulin resistance and not adequately controlled on current medications.
- Exclusion Criteria: Exclude patients with Type 1 Diabetes, significant renal or hepatic impairment, or history of adverse reactions to similar compounds.
- Stratification: Patients may be stratified based on BMI, duration of diabetes, baseline HbA1c levels, or presence of comorbidities to assess the drug's efficacy across different subgroups.
- Other characteristics that may be used to stratify patients are: disease severity, c-peptide levels, previous treatment response.
- By considering these factors we can better understand the treatment's efficacy and safety profile, paving the way for targeted and effective T2D management.


Environmental and genetic risk factors
(e.g. stress, unhealthy diet, physically inactivity, obesity, viral infection, pollution, genes: MTNR1B, TCL7F2, PPARG)
β-cell dysfunction
Insulin resistance
Gut microbiome dysbiosis
(e.g. Bifidobacterium, Bacteroides, Faecalibacterium)
Glucose homeostasis imbalance, oxidative stress, inflammation via multiple immunometabolic and signaling pathways
(e.g. Endoplasmic reticulum stress, mitochondrial dysfunction, autophagy suppression, pathways: MAPK, NKκB, TLR)
Multiple biochemistry and pathological changes
(e.g. hyperglycaemia, hyper-insulinemia, increased advanced glycated end-products, vascular & neural damage)
Symptom-based cluster A
Symptom 1
Extreme hunger
Symptom 2
Excessive thirst
Symptom 3
Unusual weight loss
Symptom 4
Fatigue
Symptom 5
Irritability
Symptom 6
Blurred vision
Symptom-based cluster B
Symptom 7
Irregular defecation
Symptom 8
Abdominal distension
Symptom 9
Gastric pain
Symptom 10
halitosis
Symptom 11
Hot flush
Symptom 13
Musculo-skeletal pain
Symptom 14
Change in tongue appearance and pulse
Symptom-based cluster C
Classical diabetes presentations
Less common presentations, potential stratifier

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THANK YOU