# BIOCHEMISTRY

# Gluconeogenesis

by
Dr Jaya Vejayan
Faculty of Industrial Sciences & Technology
email: jayavejayan@ump.edu.my

# Chapter Description

- Overview

  This pathway although can be mistaken to be direct reverse of glycolysis but differ marginally due to compartmentalization of its reaction location.

- Expected Outcomes

  You should be able to have clear understanding the differences of this pathway with glycolysis. Its contributions in regulating blood glucose.

- Other related Information

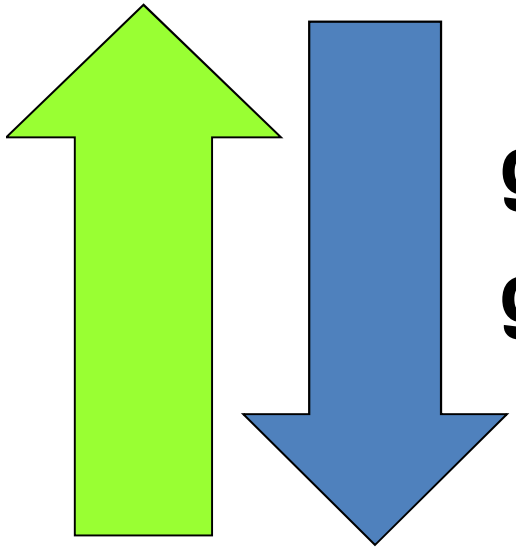
  Some relevant questions been provided for improving your understanding of the topic. You are expected to search for external sources for information to adequately answer the questions. All pictures and figures within this chapter categorized as creative commons for the purpose of education only.


**Gluconeogenesis**
**by Jaya Vejayan**
**http://ocw.ump.edu.my/course/view.php?id=485**

# Important terms of metabolic pathway

- **Metabolism:**
  - Anabolism
  - Catabolism
- Anabolic pathways
  - large molecules are synthesized from smaller precursors.
  - E.g.: synthesis of polysaccharides and protein from sugars and amino acids.
- Catabolic pathways
  - larger molecules are degraded to smaller molecules.
  - Conversion of glucose and fatty acid to $CO_2$ & water.

**Definition:** the *biosynthesis* of glucose primarily from pyruvate and its precursors.




glycolysis

gluconeogenesis

gluco neo genesis

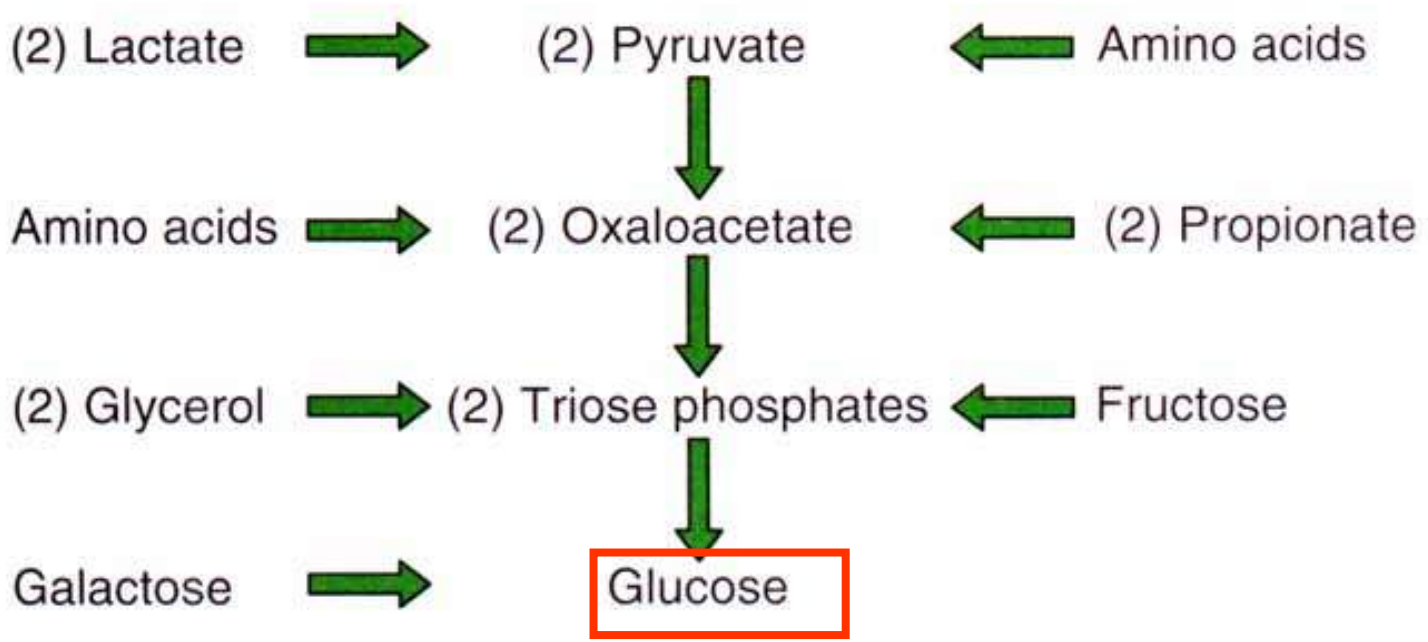
sugar

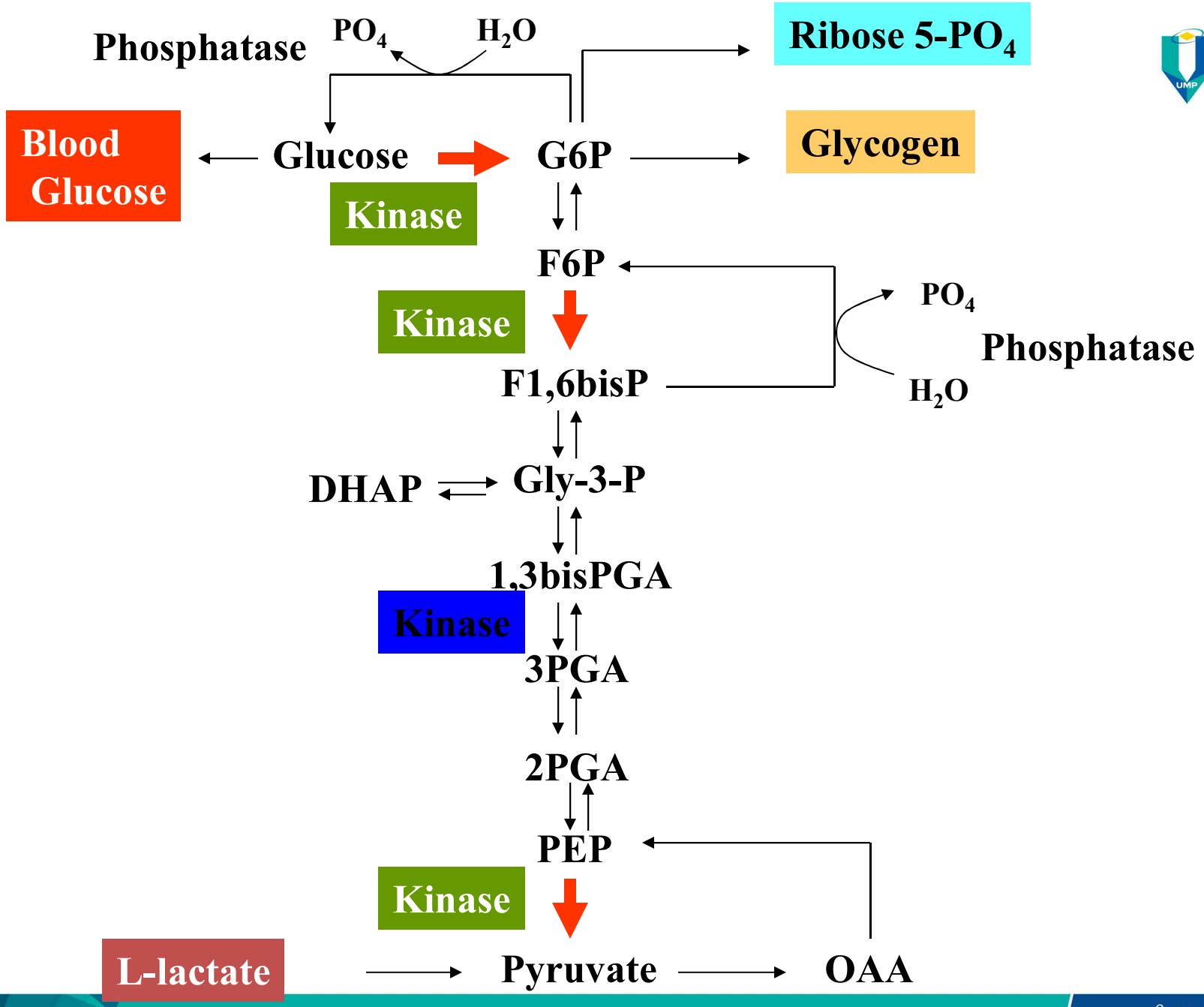
(re)new

create

# Metabolites feed into gluconeogenesis at various points

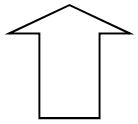
main path




Phosphatase
$PO_4$
$H_2O$
Ribose 5-$PO_4$
Blood Glucose
Glucose
G6P
Glycogen
Kinase
F6P
Kinase
$PO_4$
Phosphatase
F1,6bisP
$H_2O$
DHAP
Gly-3-P
1,3bisPGA
Kinase
3PGA
2PGA
PEP
Kinase
L-lactate
Pyruvate
OAA

# Irreversible glycolytic steps bypassed

| GLYCOLYSIS | GLUCONEOGENESIS |
| --- | --- |
| 1. Hexokinase (hexK) | by Glucose-6-phosphatase |
| 2. Phosphofructokinase-1 (PFK-1) | by Fructose 1,6-bisphosphatase (FBP-1) |
| 3. Pyruvate kinase (PyrK) | by Pyruvate Carboxylase & Phosphoenolpyruvate carboxykinase (PEPCK) |



**These 3 key enzymes**

# Gluconeogenesis

## Synthesis of glucose de novo (from scratch)

**An anabolic pathway for the synthesis of glucose from L-lactate or smaller precursors.**

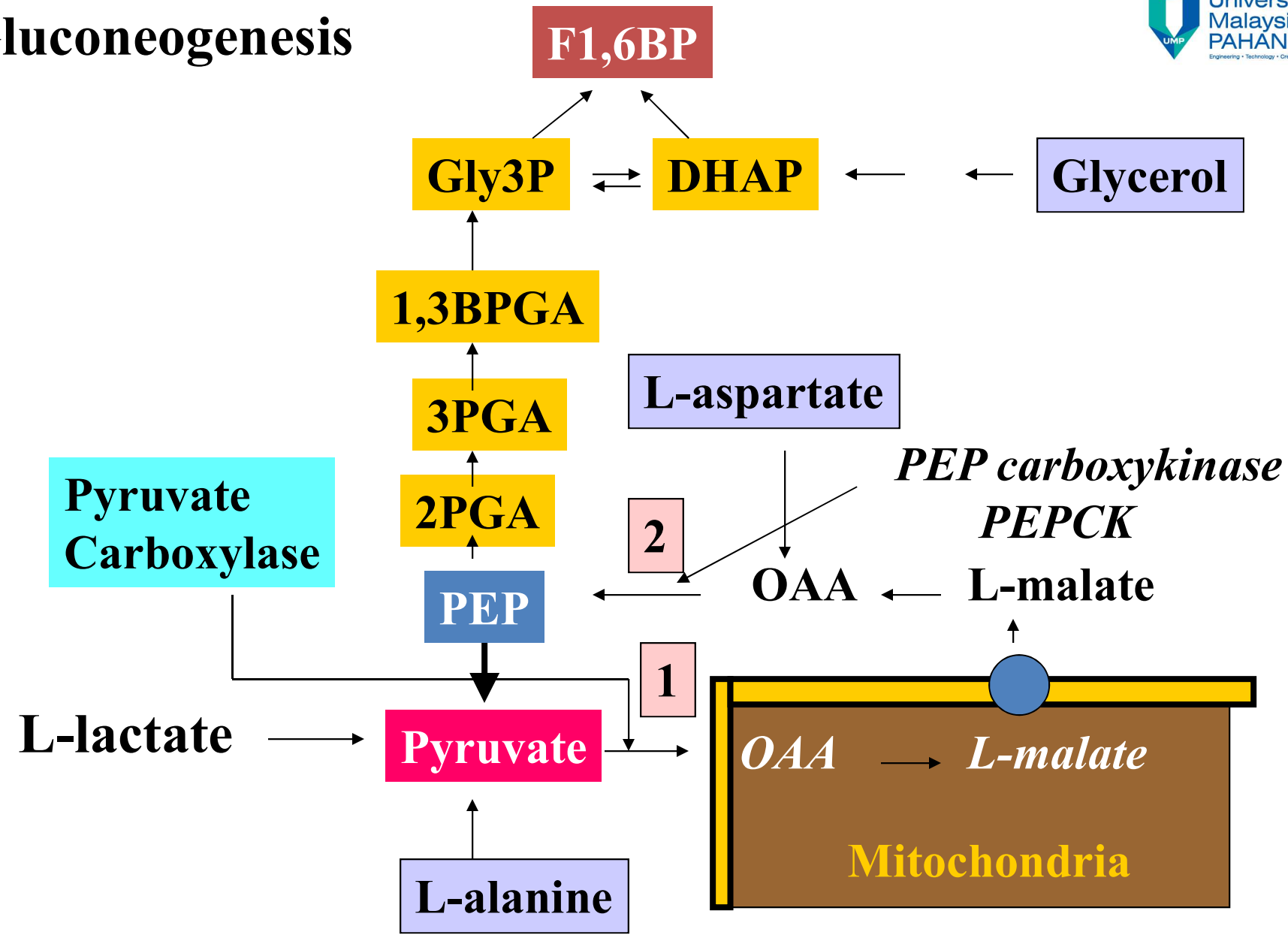
## Significance:

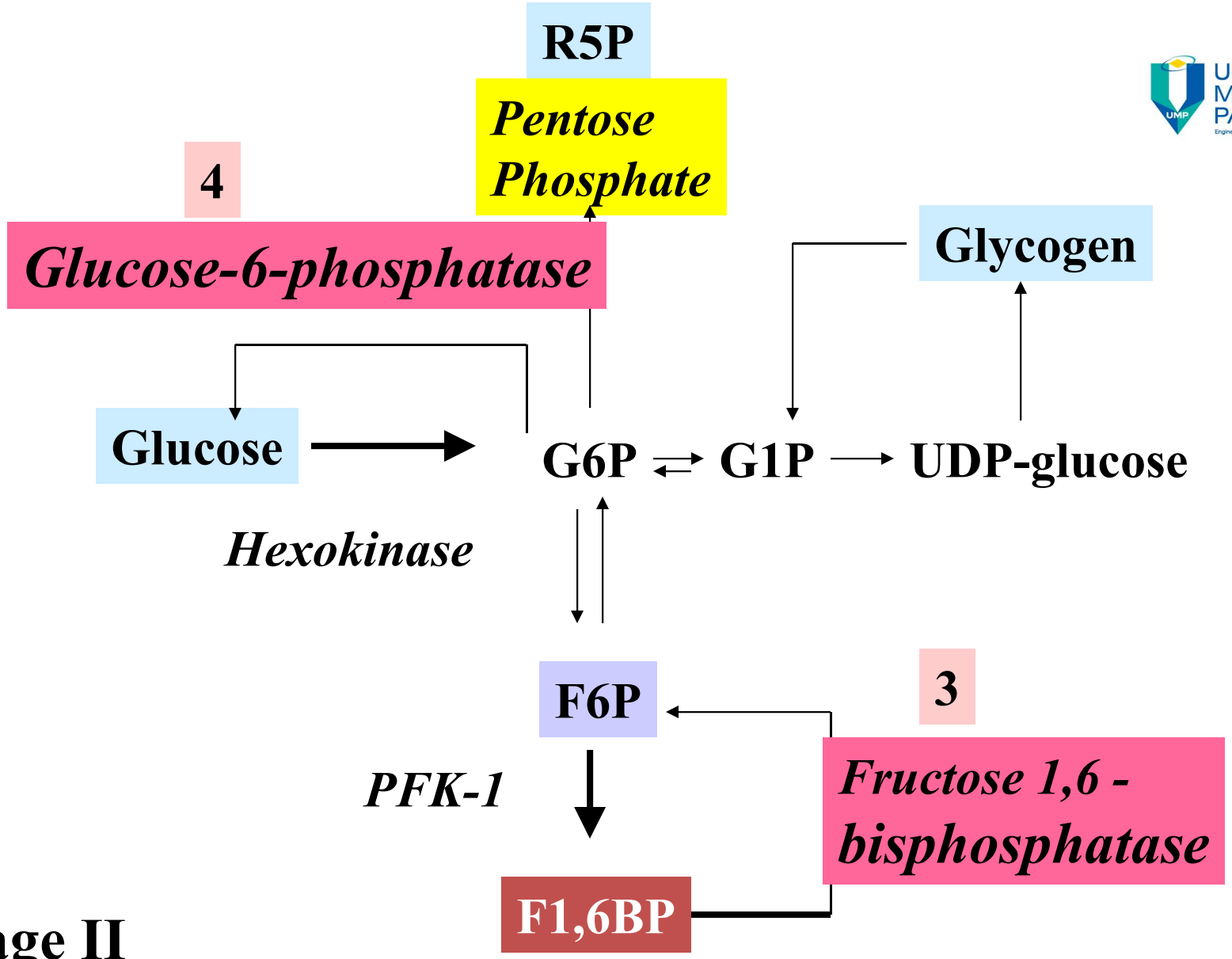
**Primarily in the liver (80%); kidney (20%)**

**Maintains blood glucose levels**

**The anabolic arm of the Cori cycle**

# Stage I
# Gluconeogenesis






# Stage II Gluconeogenesis

**Problems: 3 irreversible reactions**

PEP ⟶ Pyruvate $\Delta G^{o'} = -61.9$ kJ per mol

F-1,6 bis$PO_4$ ⟶ F-6-$PO_4$ $\Delta G^{o'} = -17.2$ kJ per mol

Glucose-6-$PO_4$ ⟶ Glucose $\Delta G^{o'} = -20.9$ kJ per mol

**Take home: Gluconeogenesis feature enzymes that bypass 3 irreversible KINASE steps**

# Why do we produce glucose?

a)Need to maintain glucose levels within a narrow range in blood especially between meals.

b)Some tissues- brain, erythrocytes, and muscles in exertion use glucose at a rapid rate and sometimes require glucose in addition to dietary glucose.

c)The brain uses mostly glucose and erythrocytes can use *only* glucose as a source of energy.

- The liver comes to rescue. The *liver* is the major location for gluconeogenesis.

- The major precursor for glucose biosynthesis is pyruvate.

## What are the sources of pyruvate precursor?

- ***lactate*–from muscle, forms pyruvate**
- **some *amino acid* carbon skeletons- from diet or breakdown of muscle protein during starvation- most important is alanine**
- ***TCA cycle intermediates***
- ***propionate* from breakdown of certain fatty acids and amino acids.**
- ***glycerol* from certain lipids.**

◆ *Lactate* is the primary source for pyruvate.

-- In muscle, lactate is produced in great quantities during exertion (cause of muscle Ache felt after an exercise).

-- This excess lactate cannot be further oxidized in muscle.

-- Lactate is released from the muscles to the blood and travels to the *liver* for conversion to pyruvate and, ultimately to glucose.

☛Notice glucose cannot be made from acetyl CoA

# Lactate – taken up by the liver (Cori cycle)

- In liver – **gluconeogenesis** occurs (lactate to pyruvate to glucose).

- **Muscular activity stop:**
  - Glucose is used to supplies of glycogen through **glycogenesis**.

- **Cori cycle** – prevent of **lactic acidosis** in muscle under anaerobic conditions.

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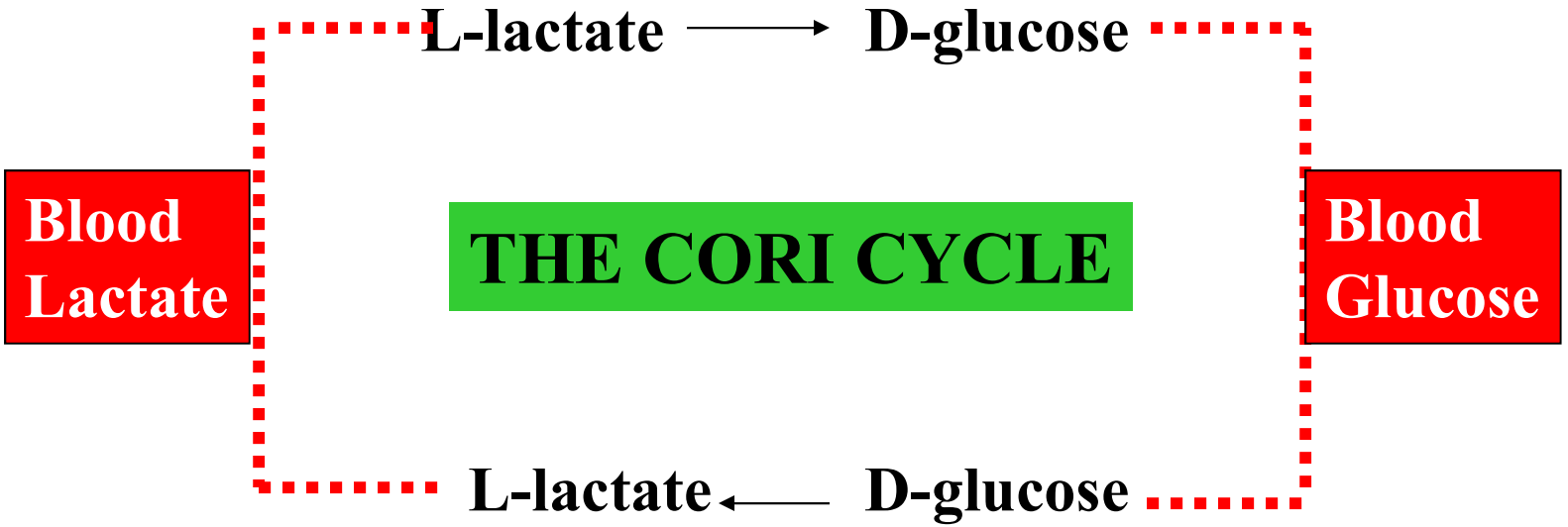
# Liver is a major anabolic organ




# Muscle is a major catabolic tissue

# Starvation/Fasting

The **source of pyruvate and oxaloacetate** for gluconeogenesis during fasting or carbohydrate starvation is mainly **amino acid catabolism**.

Some amino acids are catabolized to pyruvate, oxaloacetate, or precursors of these.

**Muscle proteins** may break down to supply amino acids. These are transported to liver where they are deaminated and converted to gluconeogenesis inputs.

**Glycerol**, derived from hydrolysis of triacylglycerols in fat cells, is also a significant input to gluconeogenesis.

# REGULATION

**FOCUS ON CARBON FLOW**

**L-lactate ⟶ Glucose (Synthesis)**
**Glucose ⟶ Pyruvate (Degradation)**

**ENZYMES (Allosteric, cAMP-dependent, organ-specific isozymes)**

***Rule 1. Allosteric are targets of metabolite regulators (effectors)***

***Rule 2. Kinases in glycolysis; phosphatases in synthesis***

**Exception: PEPCK in synthesis - cAMP**

**POSITIVE EFFECTORS**

***Rule 3. ATP, citrate, acetyl-CoA, G6P turn on synthesis***
***AMP, F2,6BP,turn on degradation***

**NEGATIVE EFFECTORS**

***Rule 4. ATP, citrate, acetyl-CoA, G6P turn off degradation***
***AMP, F2,6BP turn off synthesis***

**RECIPROCAL REGULATION**

**Glycolysis** & **Gluconeogenesis** are **both spontaneous**.
If both pathways were simultaneously active in a cell, it would constitute a "**futile cycle**" that would waste energy.

**Glycolysis:**

**glucose + 2 $NAD^+$ + 2 ADP + 2 $P_i$ →**
**2 pyruvate + 2 NADH + 2 ATP**

**Gluconeogenesis:**

**2 pyruvate + 2 NADH + 4 ATP + 2 GTP →**
**glucose + 2 $NAD^+$ + 4 ADP + 2 GDP + 6 $P_i$**

**Questions:**

1. **Glycolysis** yields **how many ~P** ?
2. **Gluconeogenesis** spends **how many ~P** ?
3. A **futile cycle** of both pathways would waste **how many ~P per cycle** ?

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