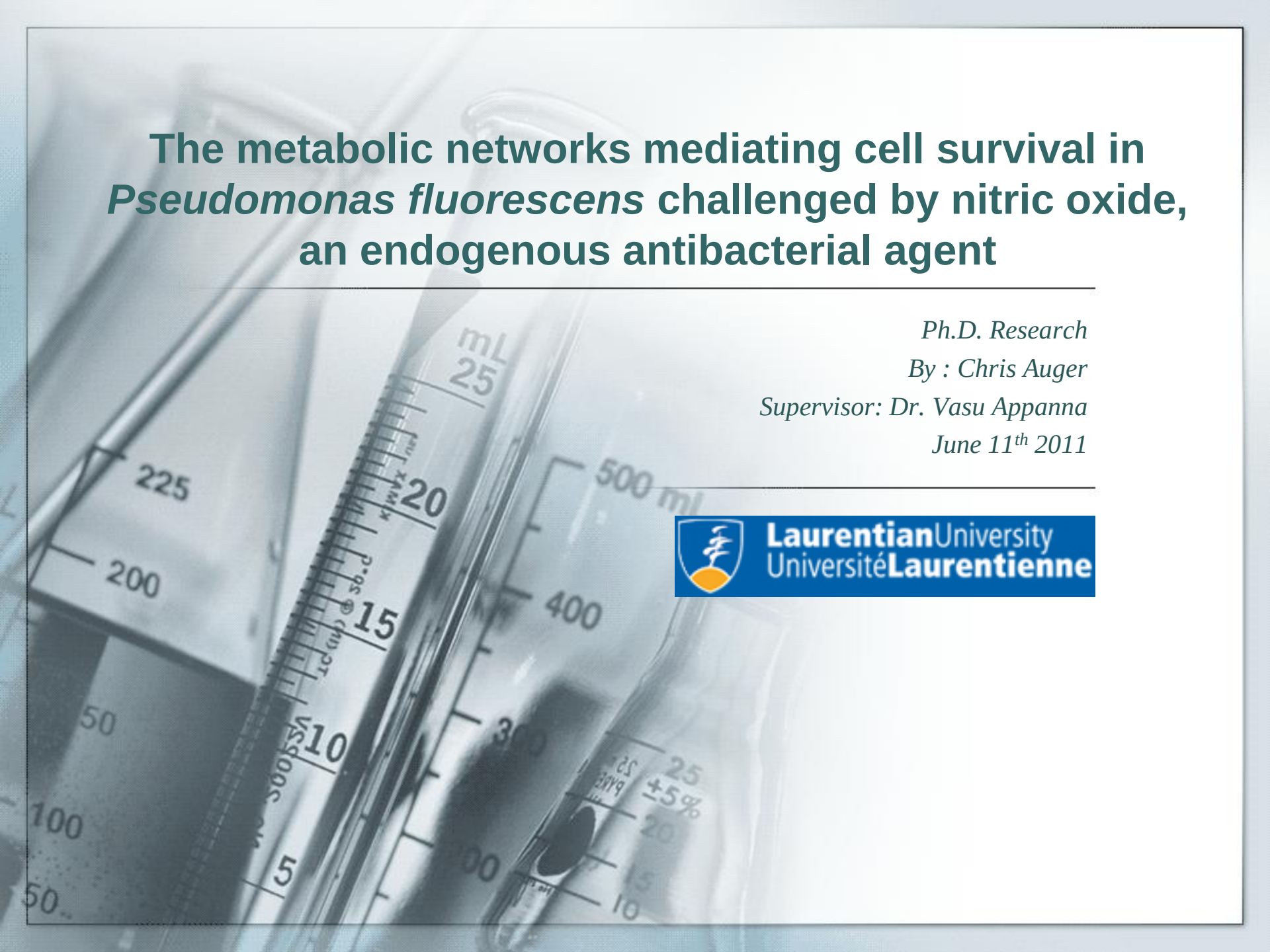
The metabolic networks mediating cell survival in *Pseudomonas fluorescens* challenged by nitric oxide, an endogenous antibacterial agent

Ph.D. Research

By : Chris Auger

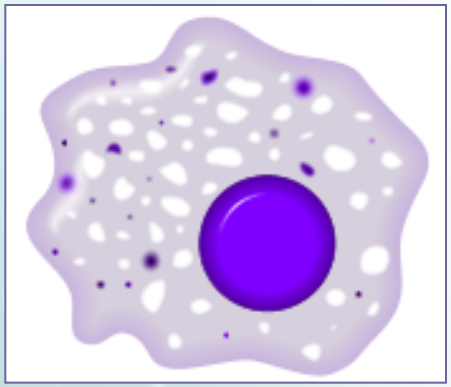
Supervisor: Dr. Vasu Appanna

June 11th 2011



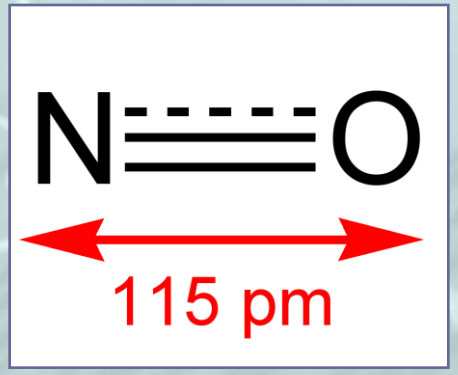
Outline

Problem statement



Immunity

Results

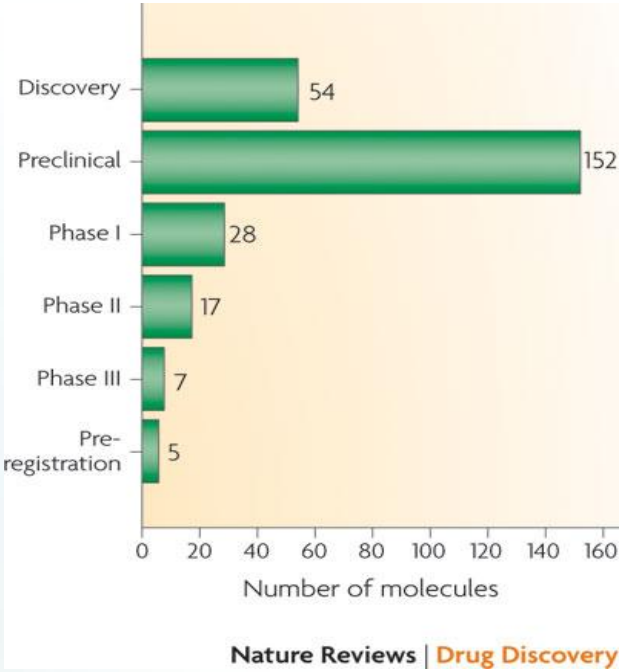


Introduction

Applications

Problem statement

- Current pipeline
- Drugs targeting gram-negative pathogens **: <u>0</u>**
- Abuse of old scaffolds



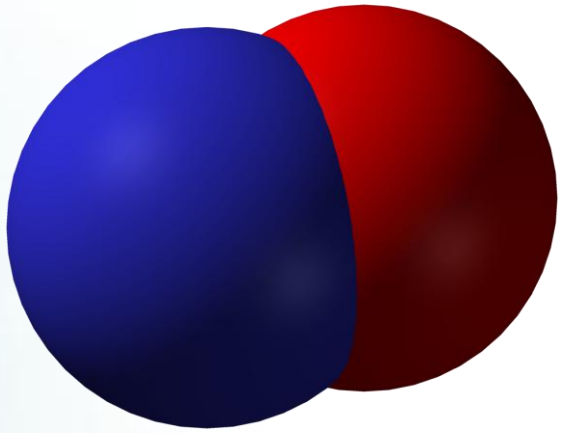
<u>Current status of antibiotic R&D activity at each development stage</u>
Source: IMS Health

"For Gram-positives we need better drugs; for Gram-negatives we need any drugs"

Dr. Brad Spellberg, author of "Rising Plague"

Nitric oxide (NO)

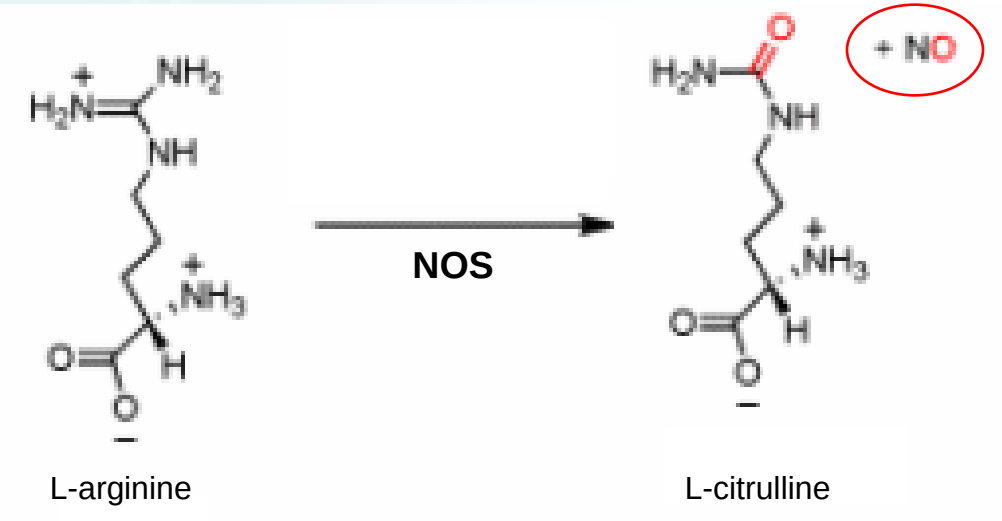
- Fat-soluble free radical
- Important signaling molecule causing vasodilation
- Industrial use



NO - Sources

Endogenous

- Enzymatic
  - NOS



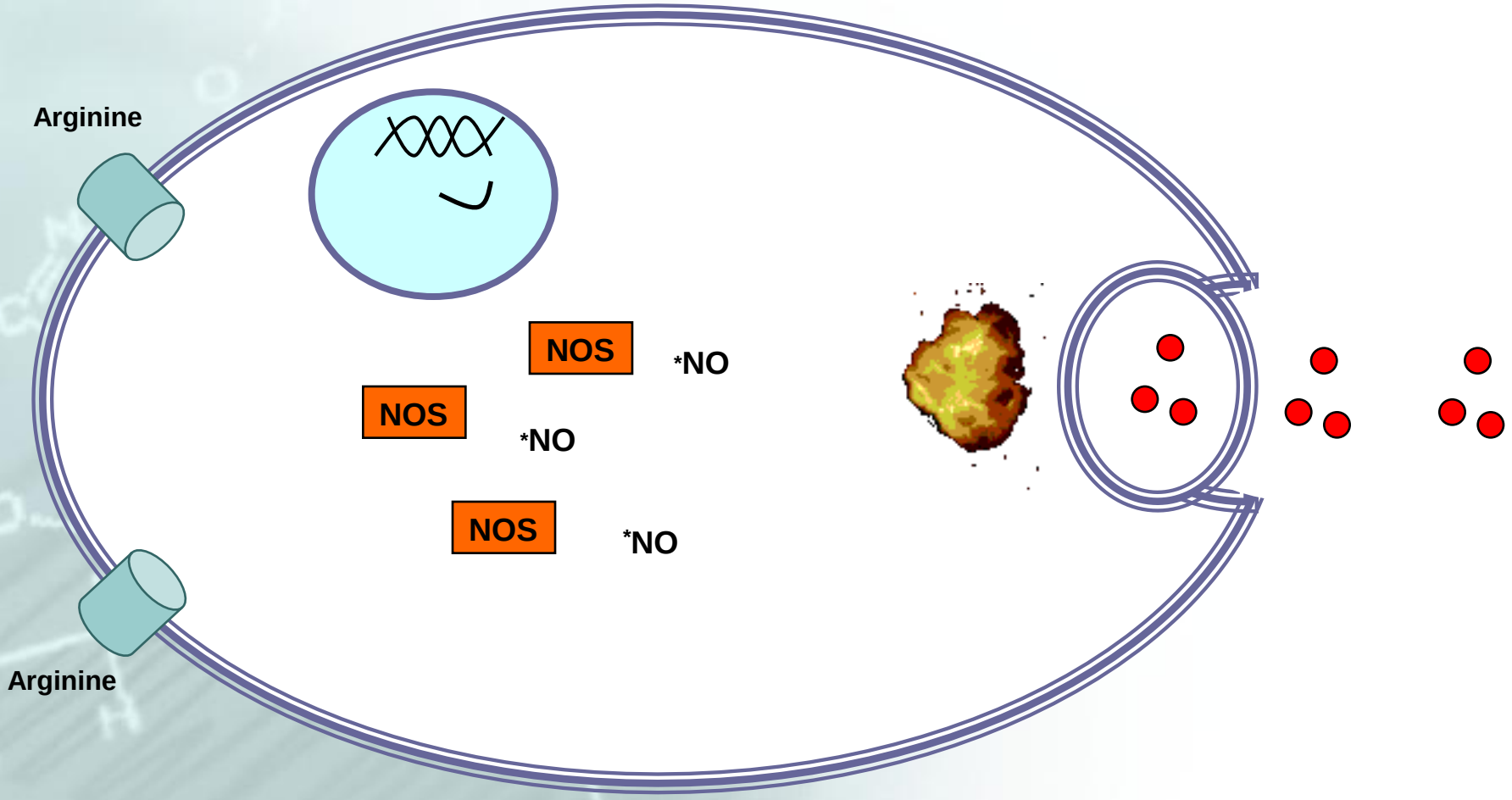
NO - Sources

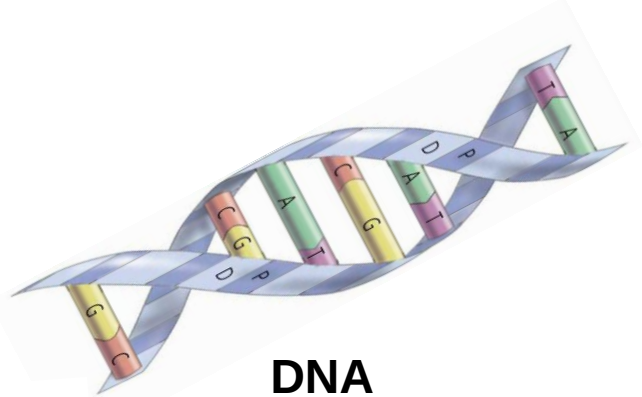
Exogenous

- Air pollutant
  - Cigarette smoke
  - Exhaust from automobile engines
  - Fossil-fuel burning power plants

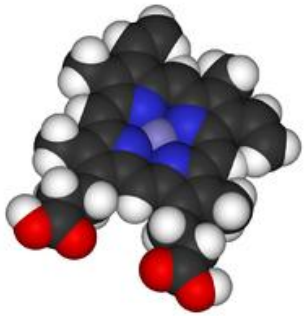
- Clinical
  - Nitroglycerin
  - SNP

NO - Immunity



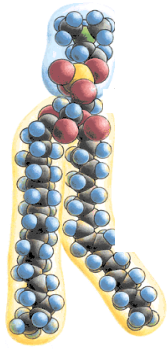


DNA

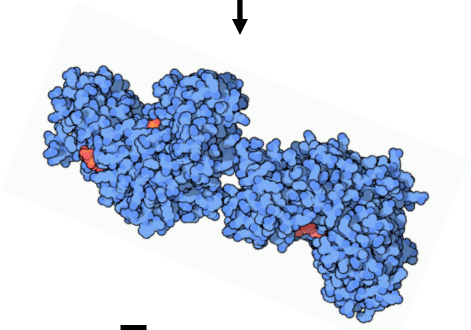


Heme

•NO



Lipids



Enzymes

Research

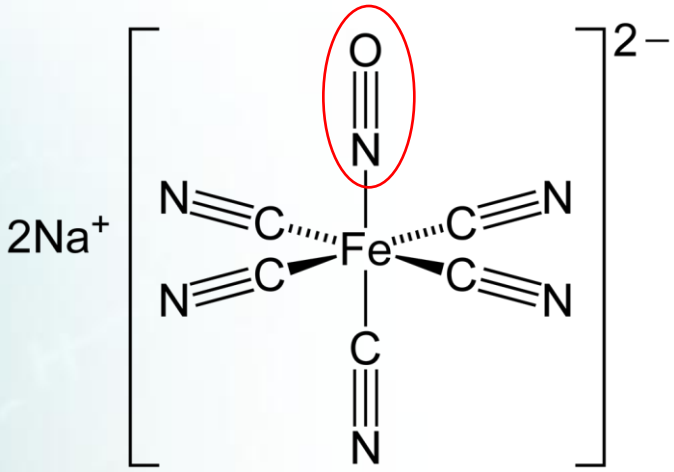
What role does metabolism play in detoxification and survival when cells are stressed by NO?

Scanning electron micrograph of *Pseudomonas fluorescens*

- Pseudomonas fluorescens
  - Soil microbe
  - Innocuous
  - Versatile metabolism

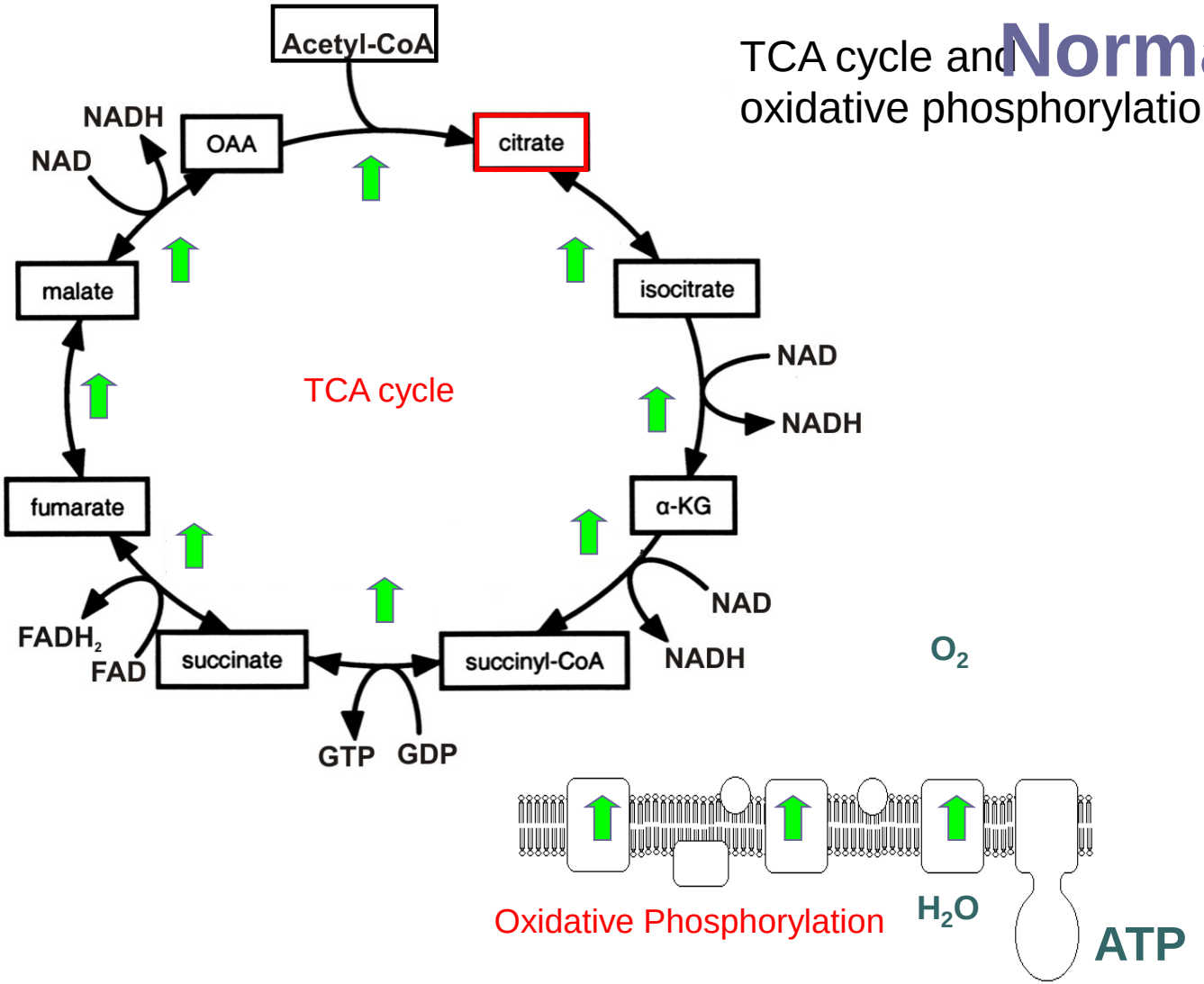
Stressing Agent

- Sodium nitroprusside (SNP)
- Potent Vasodilator. Common NO donor



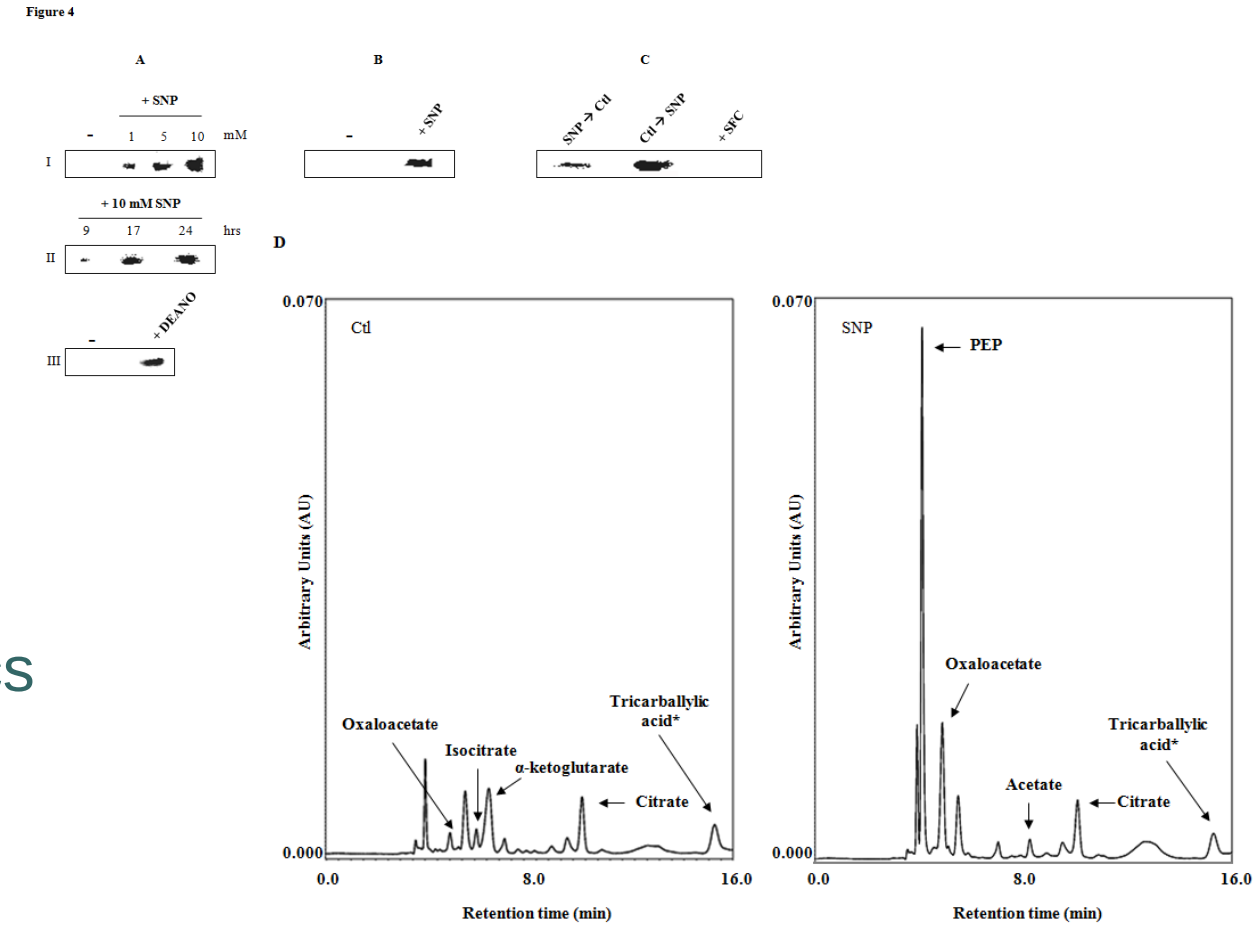
Results

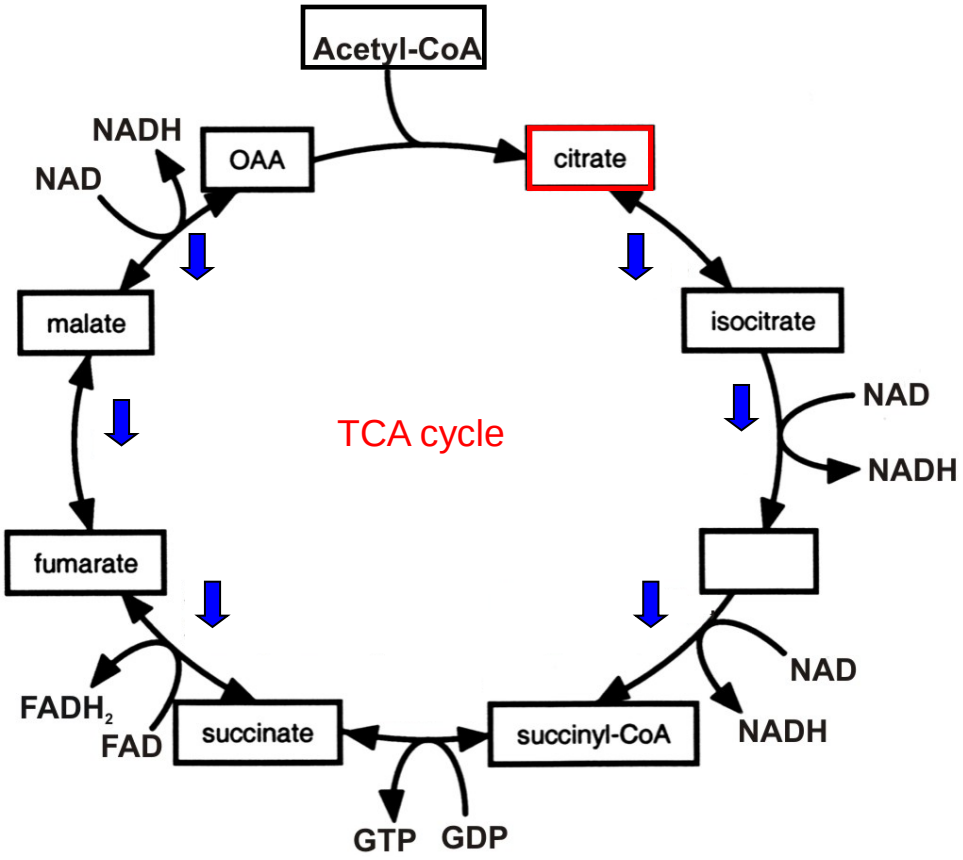
TCA cycle and oxidative phosphorylation **Normal**



Our approach

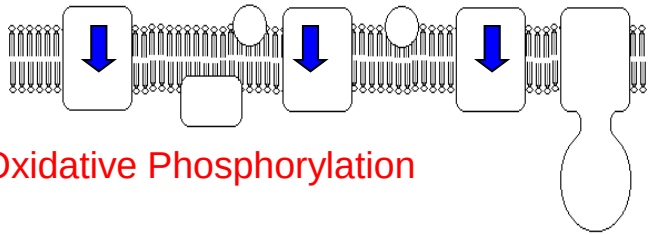
- Metabolomics
- Proteomics



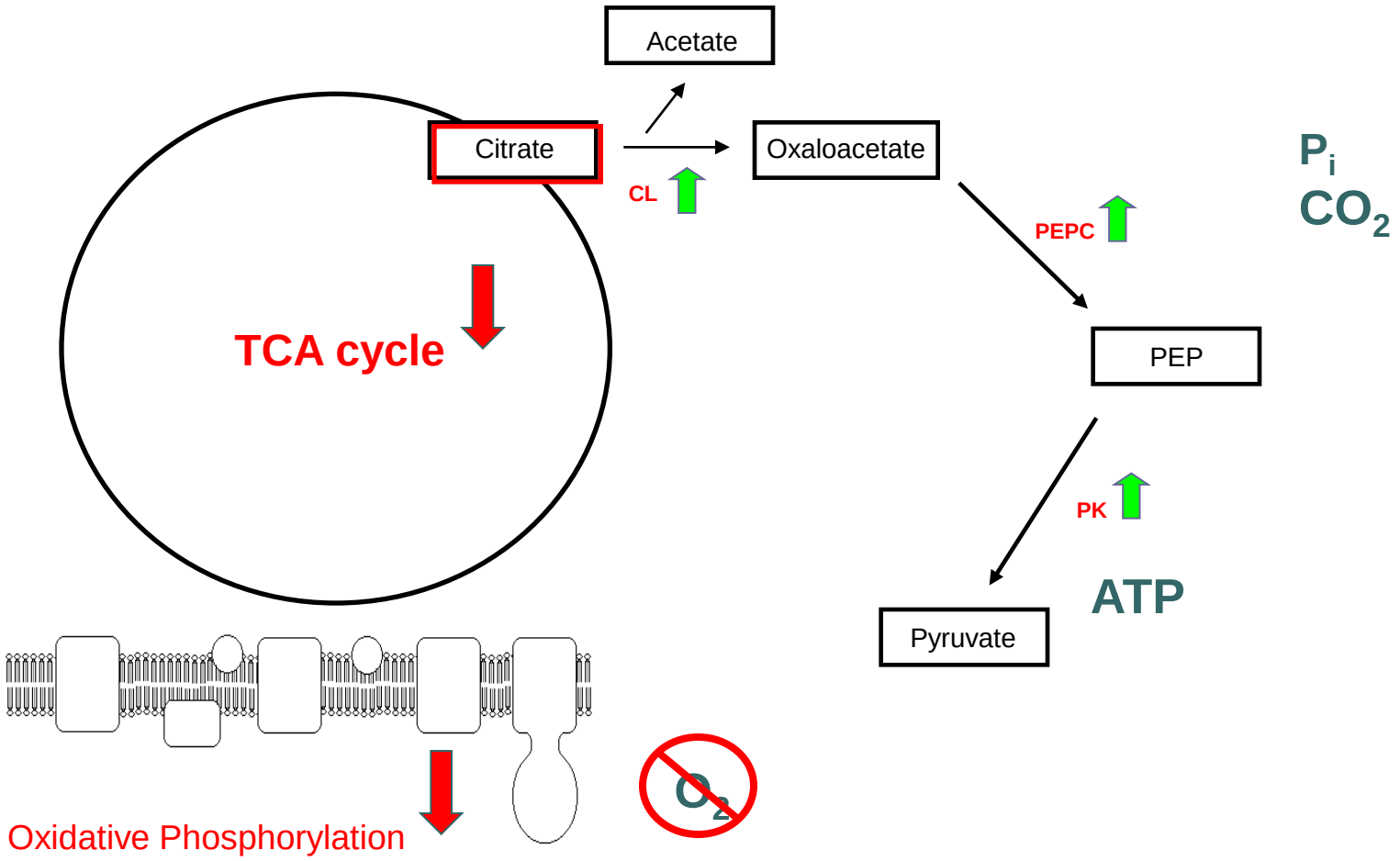


- NO

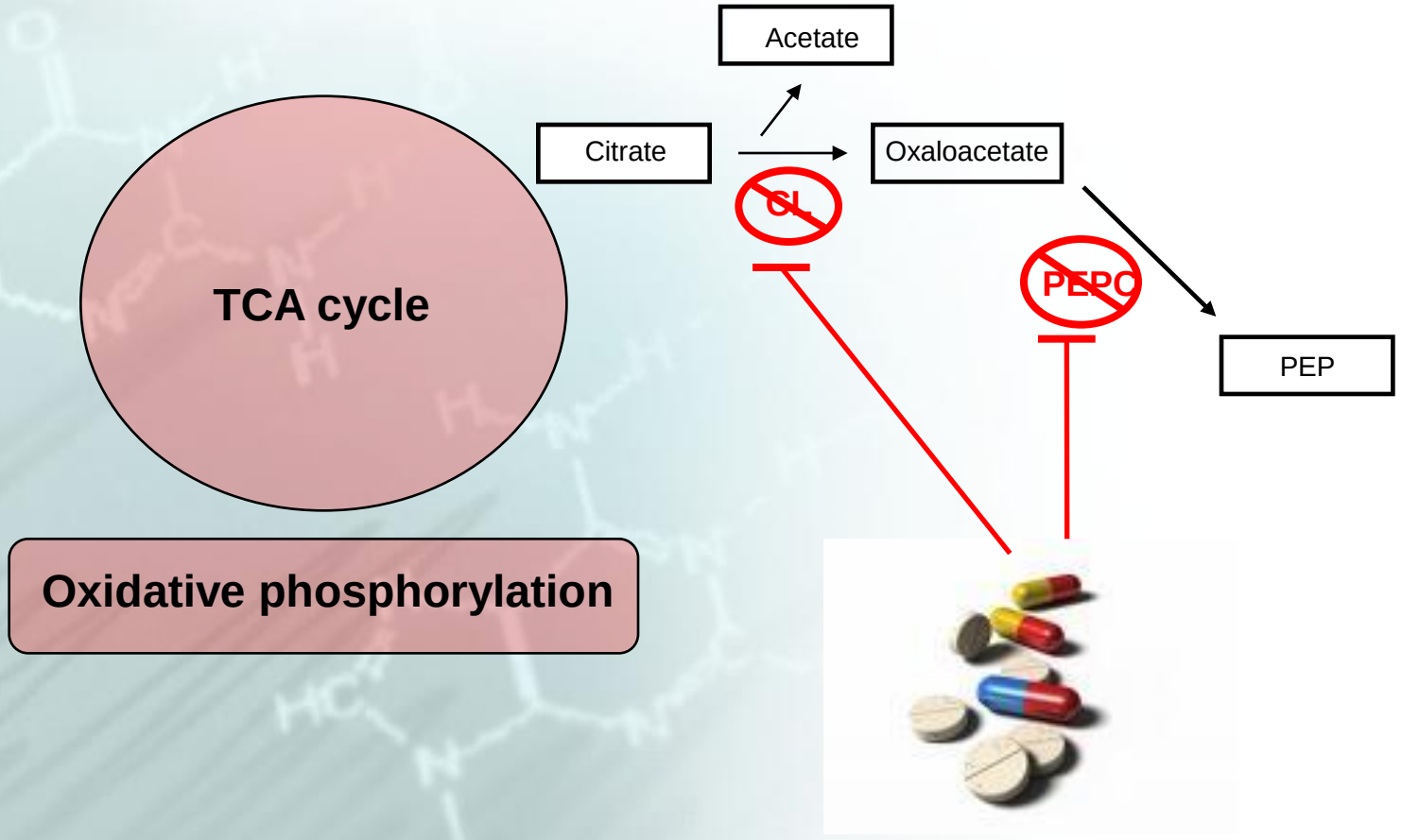
ATP



Oxidative Phosphorylation


Acetate
Citrate
Oxaloacetate
CL
PEPC
P_i
CO_2
TCA cycle
PEP
PK
ATP
Pyruvate
O_2
Oxidative Phosphorylation

Applications



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Questions

References

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