# Translational Research: From Biological Discovery to Clinical Application

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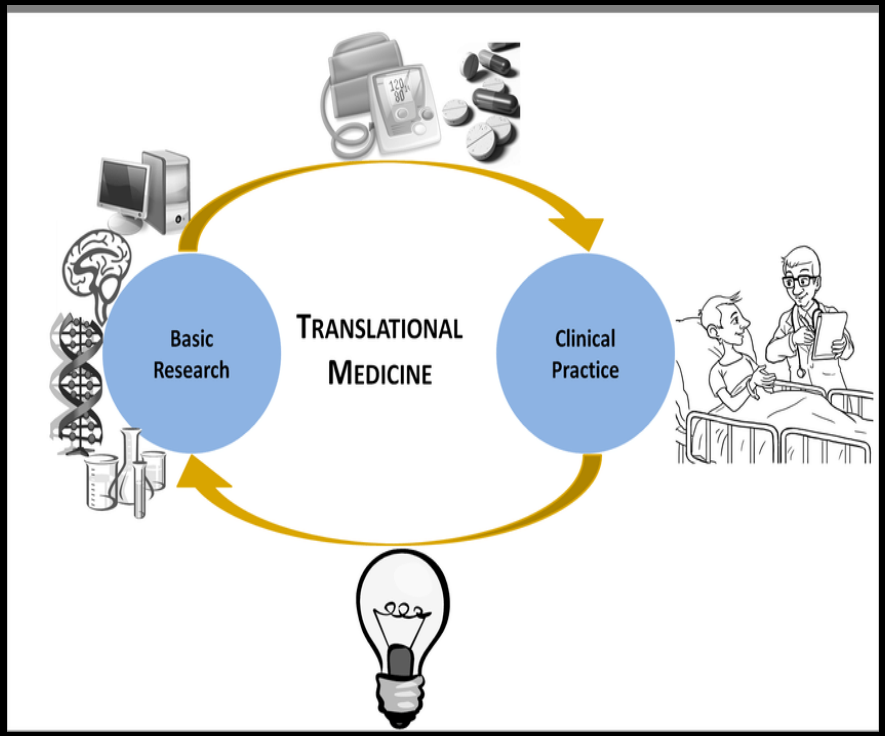
# What is Translational Research?

- Translating knowledge gained from laboratory science into clinic practice to improve health.

- Taking clinical observations back to the lab to study in depth.

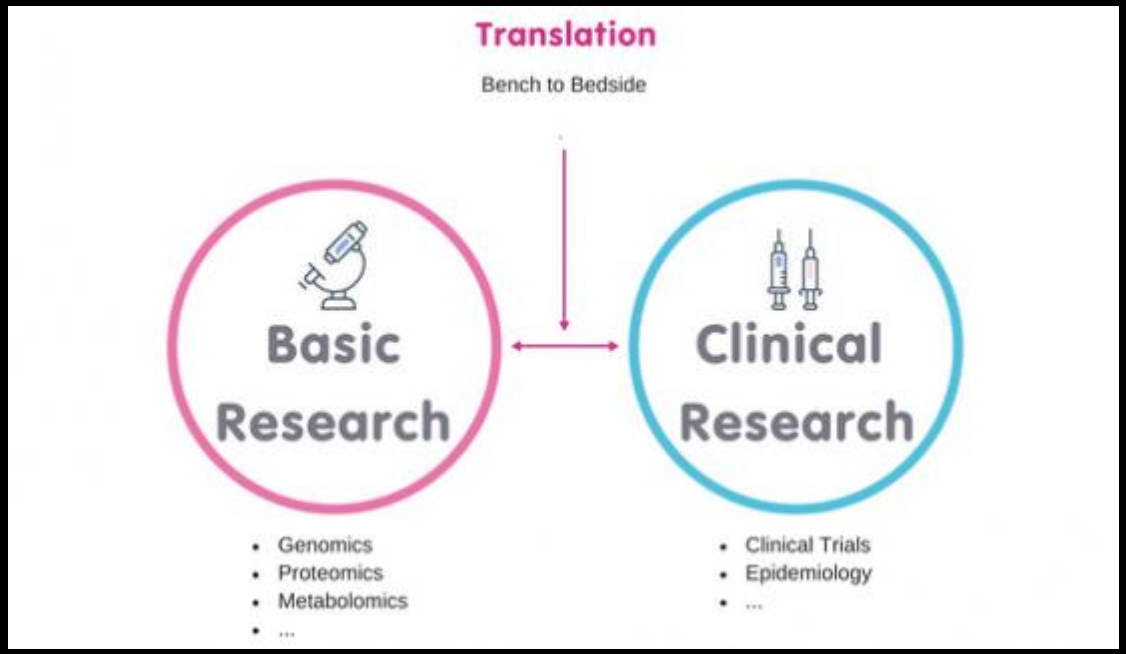


# The Aim of Translational Research is to Produce New:

- Therapeutics
- Medical devices
- Tools for diagnosing disease
- Avenues for community engagement research

# The Translational Research

- The National Institutes of Health (NIH) have made it a central priority, part of their “Roadmap” initiative.



# The Translational Research

- One of the most significant motivations comes from a relatively small number of studies that show that it takes a long time to move basic scientific ideas to practice and health impacts.

- It takes an estimated average of 17 years for only 14% of new scientific discoveries to enter day-to-day clinical practice.

# The Translational Research

- This time lag is seen as too long, certainly longer that necessary.
- Must be a better way to move research to practice more quickly without sacrificing quality or increasing costs.

# The Translational Research Continuum

**Translational Research**

***Physician-Scientist***


**Basic Biomedical Research**

**Translational From Basic Science to Human Studies**

**Clinical Science and Knowledge**

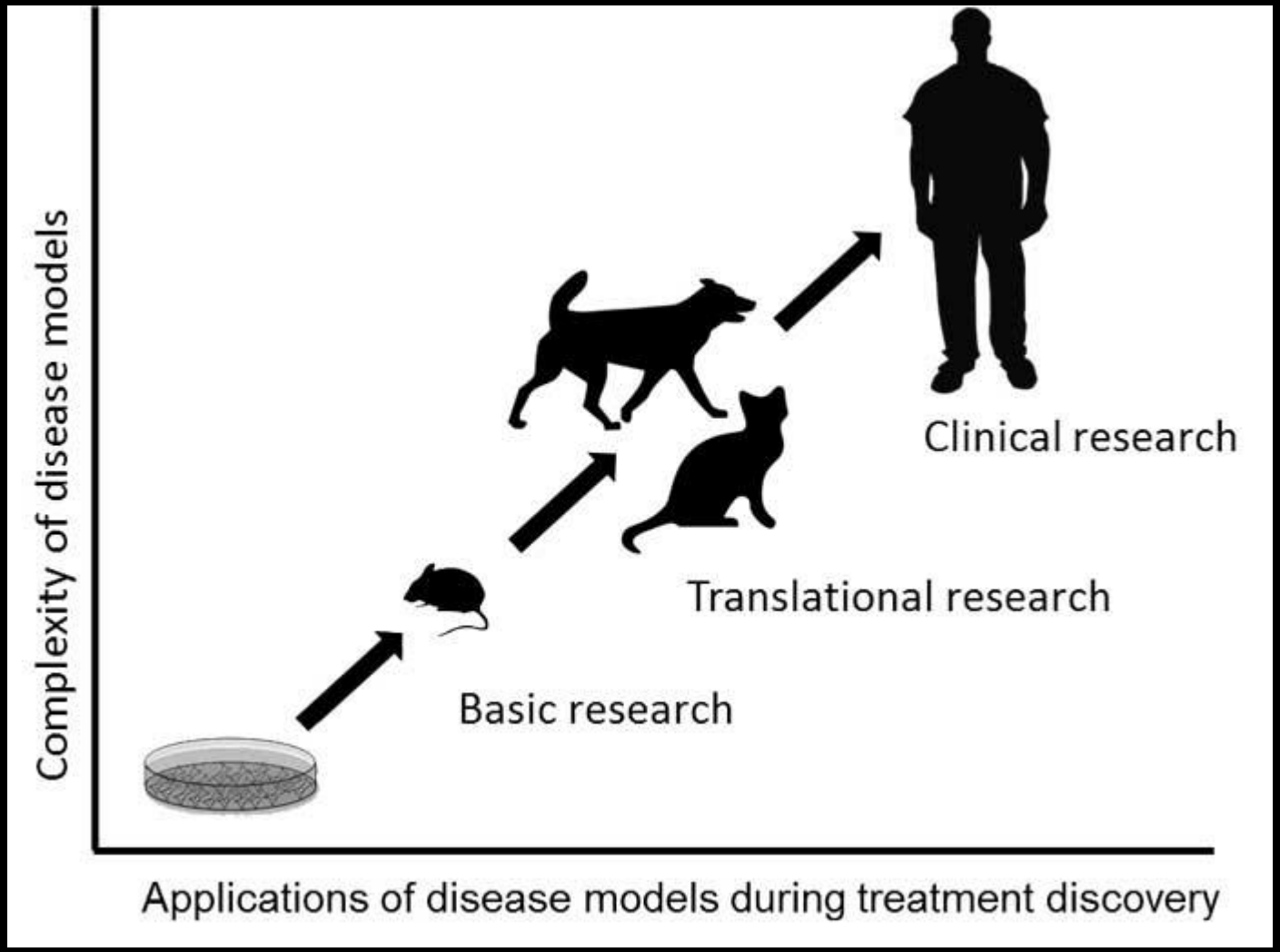
**Translational of New Knowledge into Clinical Practice and Health Decision Making**

**Improved Health**

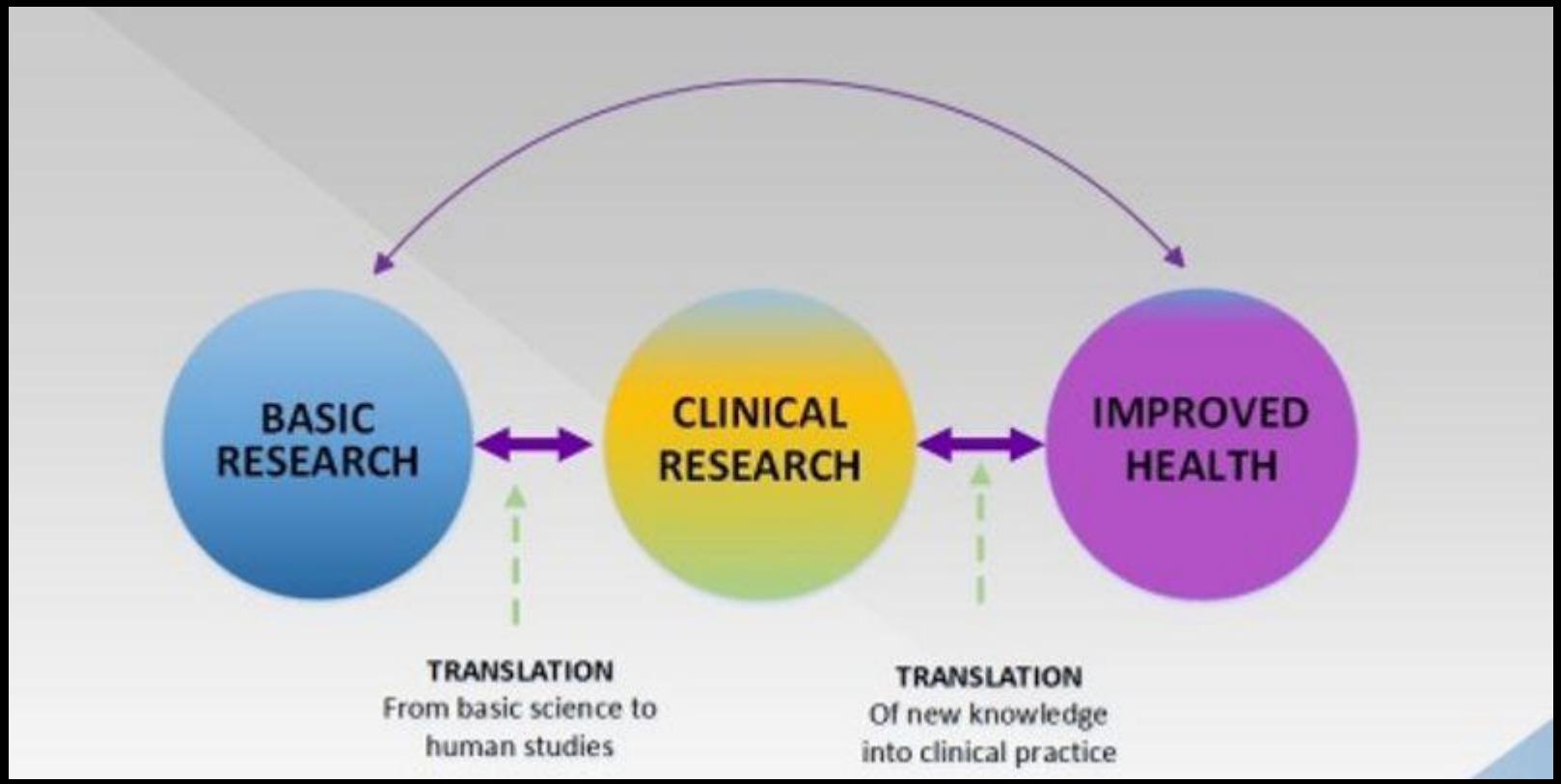
# How to Approach Design of Basic Research That is Ultimately Translatable?

- Literature review
- Design a study that uses a cell culture or animal mode that is relevant to human biology
- Treat or not treat with a drug of interest
- Document mechanism of action
- Collect data
- Clinical trials

# Laboratory of Translational Research



# Example of Translational Research Project



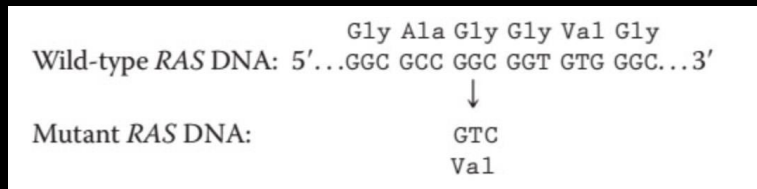
# Example I: Human Epidermal Growth Factor 2 (HER2) and Trastuzumab

# Discovering Genes Linked with Cancer

- In 1983 a group of American scientists in Robert Weinberg's group discovered the first gene associated with cancer: "Ras".

- Genes associated with cancer have been shown to promote the aggressive growth of cells (termed oncogenes).

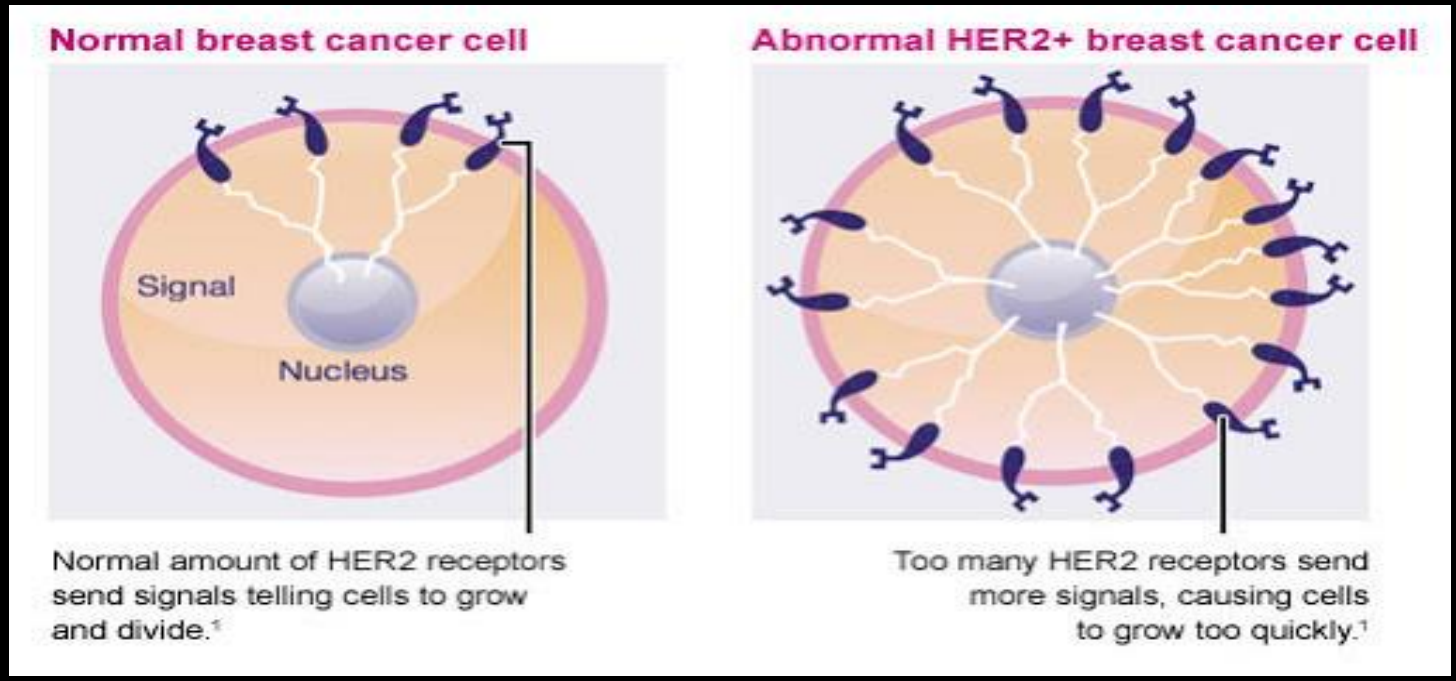
- It is important to identify these genes so that scientists could understand how tumors are formed.



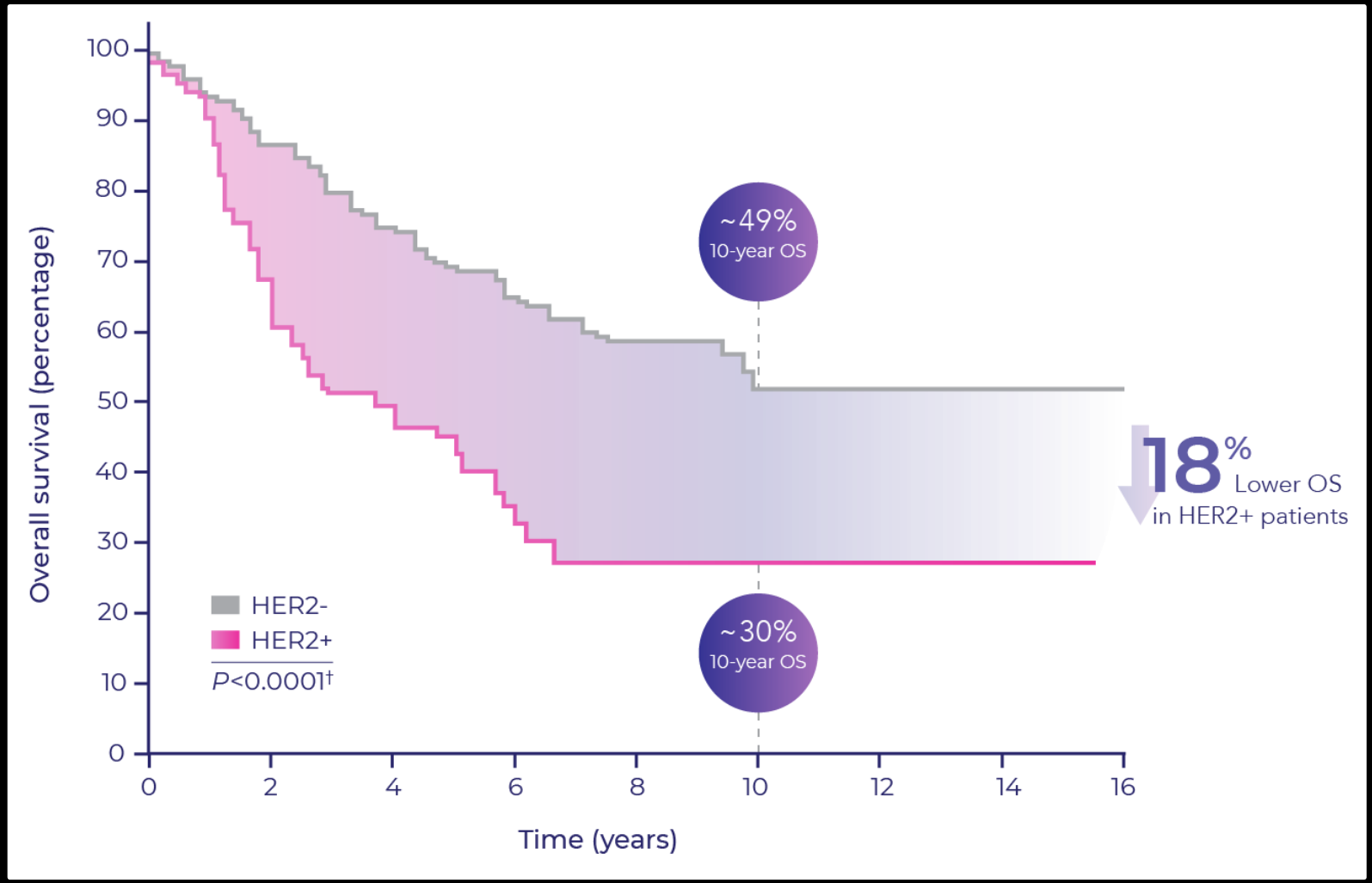
# The Human Epidermal Growth Factor Receptor 2 (HER2) Gene

- The HER2 gene was first discovered in rats in 1984 by Weinberg's group.

- The HER2 protein is  present at high levels in about 30% of breast cancers.

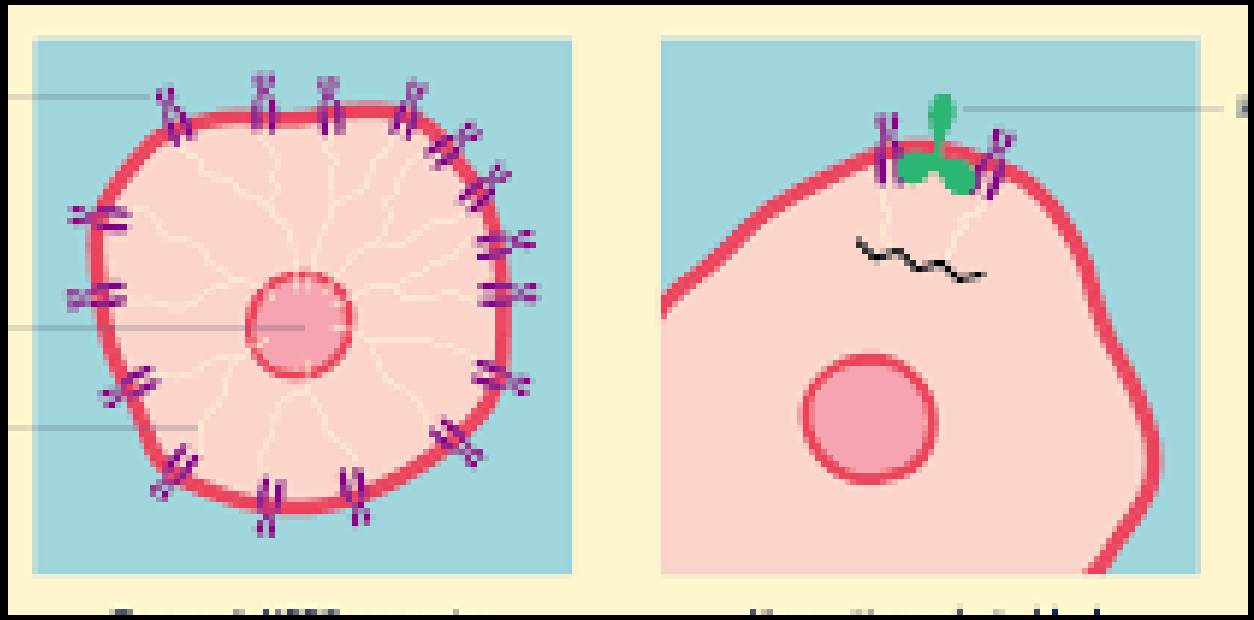


# HER2+ Status is Associated with Aggressive Breast Cancer



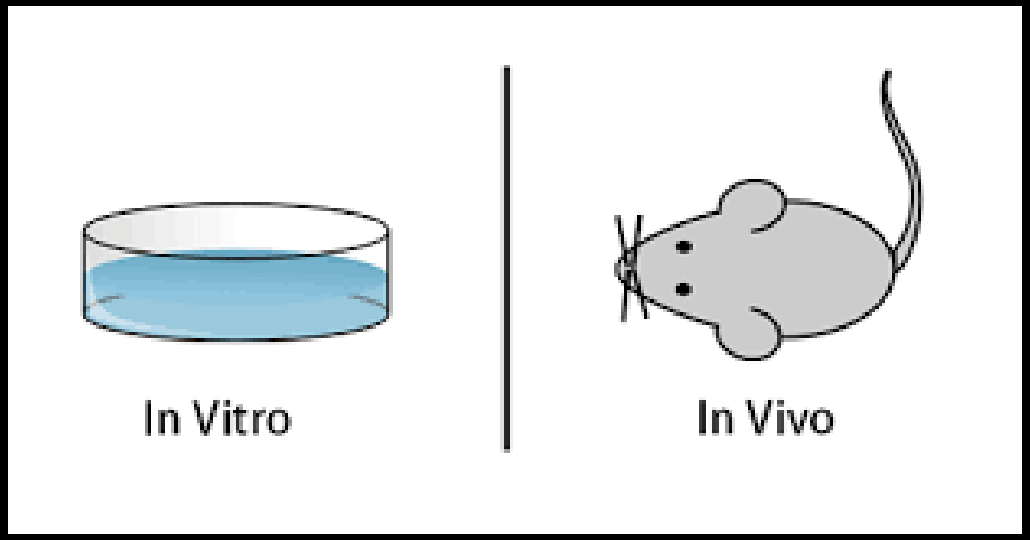
# The Breakthrough

- These findings led to researchers suggesting that if they could block the HER2 protein they could potentially slow the growth of HER2-positive breast cancer.



# The Breakthrough

- This could indeed happen in a laboratory dish.
- Then, a collaboration between Genentech and UCLA showed that the antibody could suppress the growth of HER2 positive tumors in mice.



# The Introduction of Trastuzumab

- This was then developed by Genentech to produce Trastuzumab, commercially known as Herceptin®, for human use.
- The treatment was first introduced to clinical trials in the mid 1990's for metastatic breast cancer patients that were HER2 positive.
- In 2005, five trials that involved more than 10,000 women showed that the therapy halved the recurrence rate and reduced mortality by 30%.

# Conclusions

- The use of this drug was a breakthrough in the field and improved outcomes for those with metastatic breast cancer.
- Today, over 2 million people have been treated with the drug.
- This began with the discovery of the HER2 gene and led to the development of a monoclonal antibody that targets the HER2 protein that the gene codes for.

# 2019 Lasker Awards

## Herceptin—a targeted antibody therapy for breast cancer

**H. Michael Shepard**
Genentech

**Dennis J. Slamon**
University of California, Los Angeles

**Axel Ullrich**
Max Planck Institute of Biochemistry

"For their invention of Herceptin, the first monoclonal antibody that blocks a cancer-causing protein, and for its development as a life-saving therapy for women with breast cancer"

# Example II: Acute Myocardial Infarction

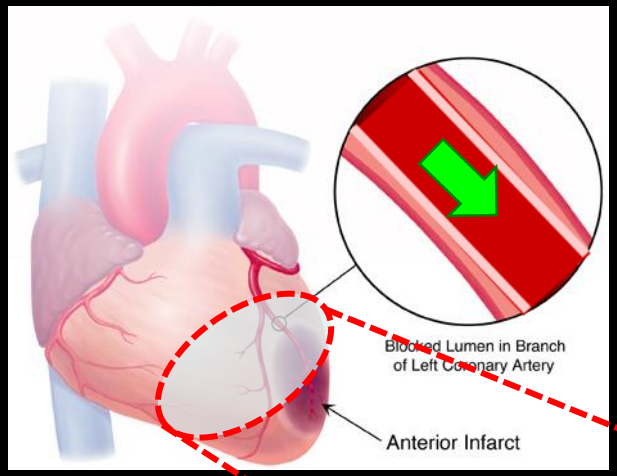
- Acute myocardial infarction is a major cause of morbidity and mortality worldwide.

- Heart disease and stroke statistics-2014 update: a report from American Heart Association

  – Approximately every 40 seconds, an American will have MI.

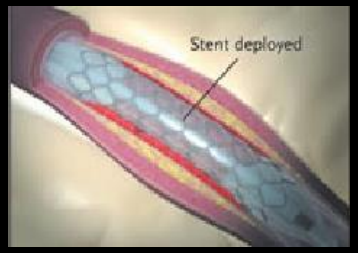
# Myocardial Reperfusion

## Acute Myocardial Infarction




## Myocardial Reperfusion

**Percutaneous coronary intervention**

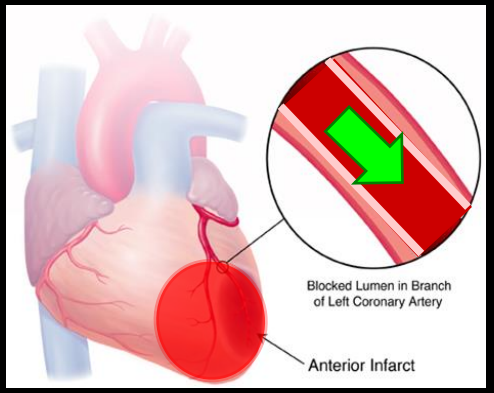



**Thrombolytic therapy**

**In absence of reperfusion**

**With reperfusion**

# Potential Manifestations of Reperfusion Injury

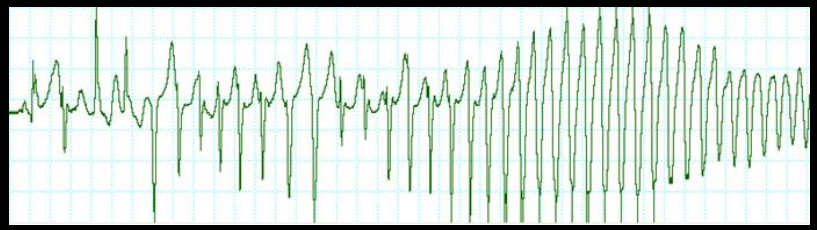



⬆ ROS & Oxidative Damage

⬇

"Ischemia/Reperfusion Injury"

# Potential Manifestations of Reperfusion Injury

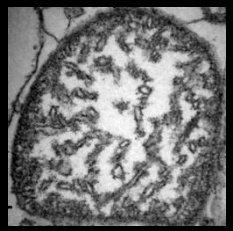


Reperfusion Arrhythmias

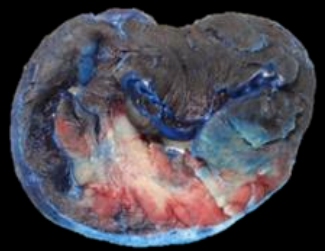
Ventricular Dysfunction

"Ischemia/Reperfusion Injury"

Mitochondrial Dysfunction



Myocardial Injury



# Cardioprotective Strategies for Reducing Lethal Reperfusion Injury

## Acute Myocardial Infarction

In absence of reperfusion

## Myocardial Reperfusion

With reperfusion

## ess Lethal Reperfusion Injury

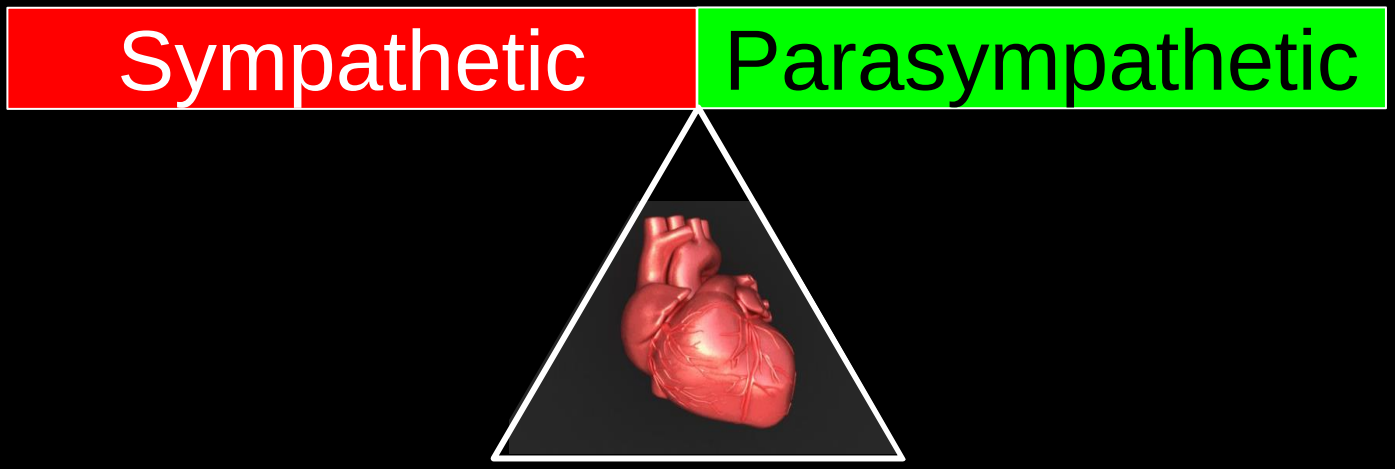
With reperfusion plus additional targeted therapy

**Cardio-Protective Strategies:**

- Ischemic conditioning
- Pharmacologic approach
- **Vagus nerve stimulation (VNS)**

# The Autonomic Nervous System

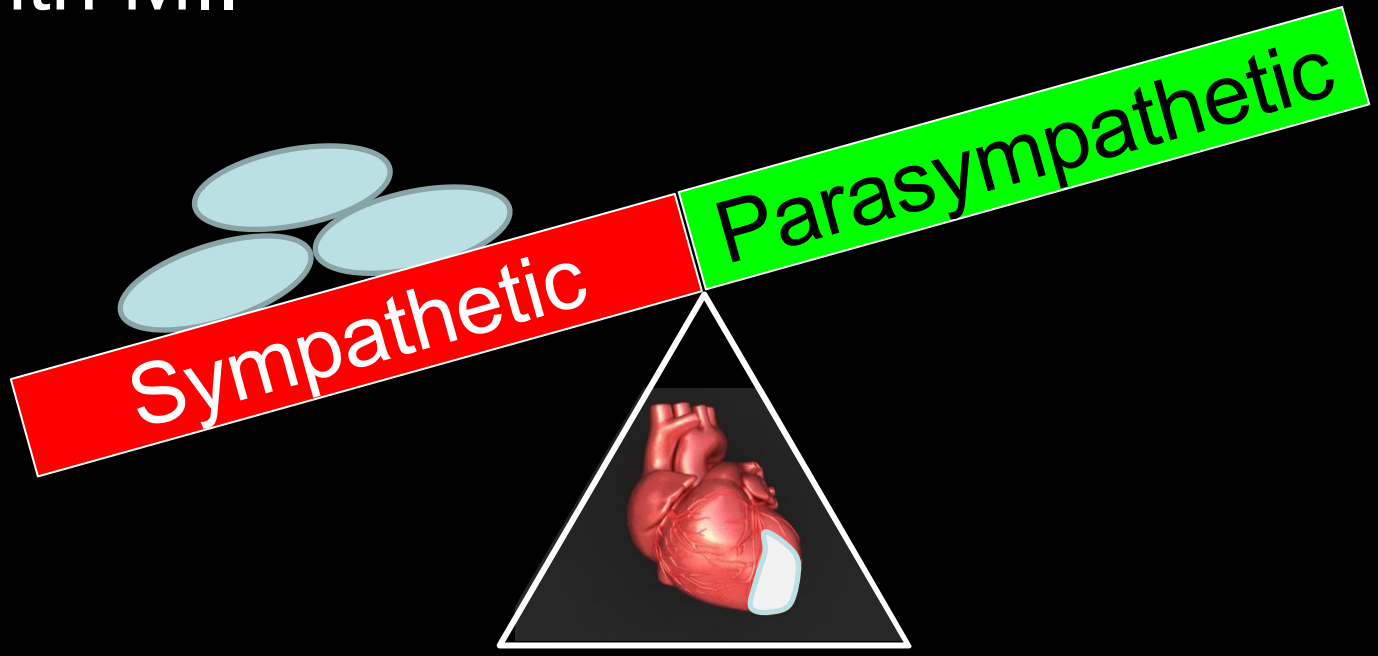
- The autonomic nervous system plays an important role in the regulation of the mammalian heart.




Levy MN et al. *Circ Res*. 1971;29:437-445

# Autonomic Imbalance in MI

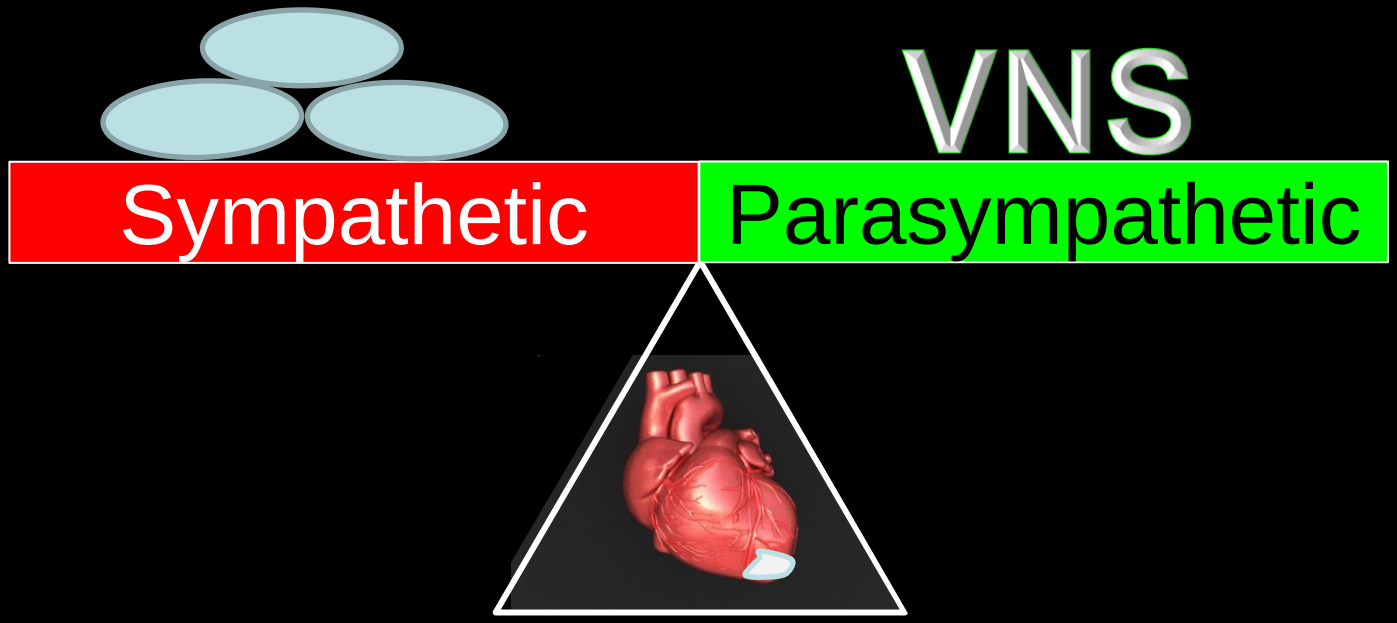
- Increased cardiac sympathetic tone and reduced vagal activity are the characteristic autonomic phenotype associated with MI.




Aidonidis I et al. *Cardiology*. 1992;80:196-204

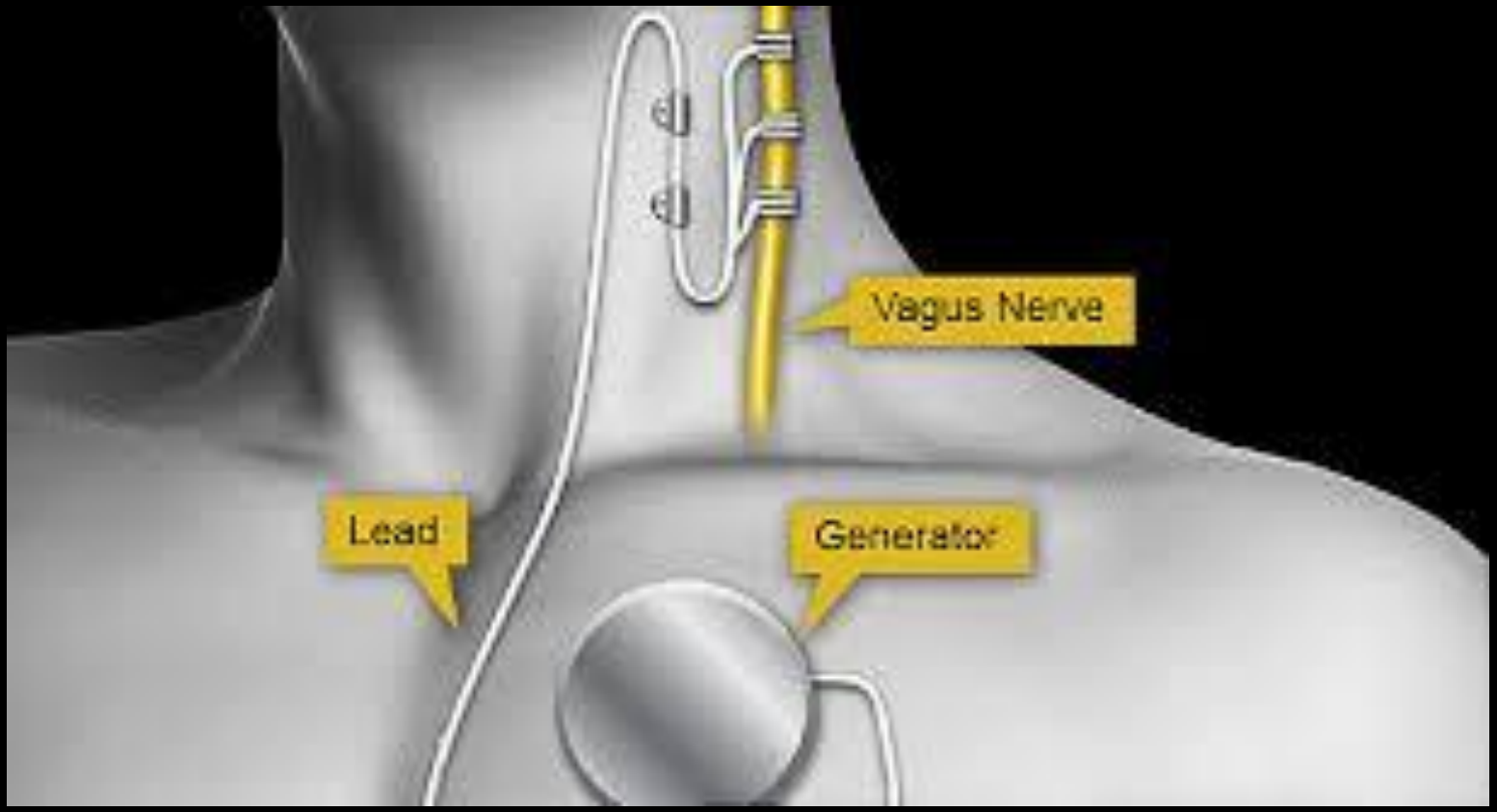
# Rebalanced Autonomic Activity

- Augmenting vagal activity by vagus nerve stimulation (VNS) may be a potential therapeutic intervention for the affected MI patients.

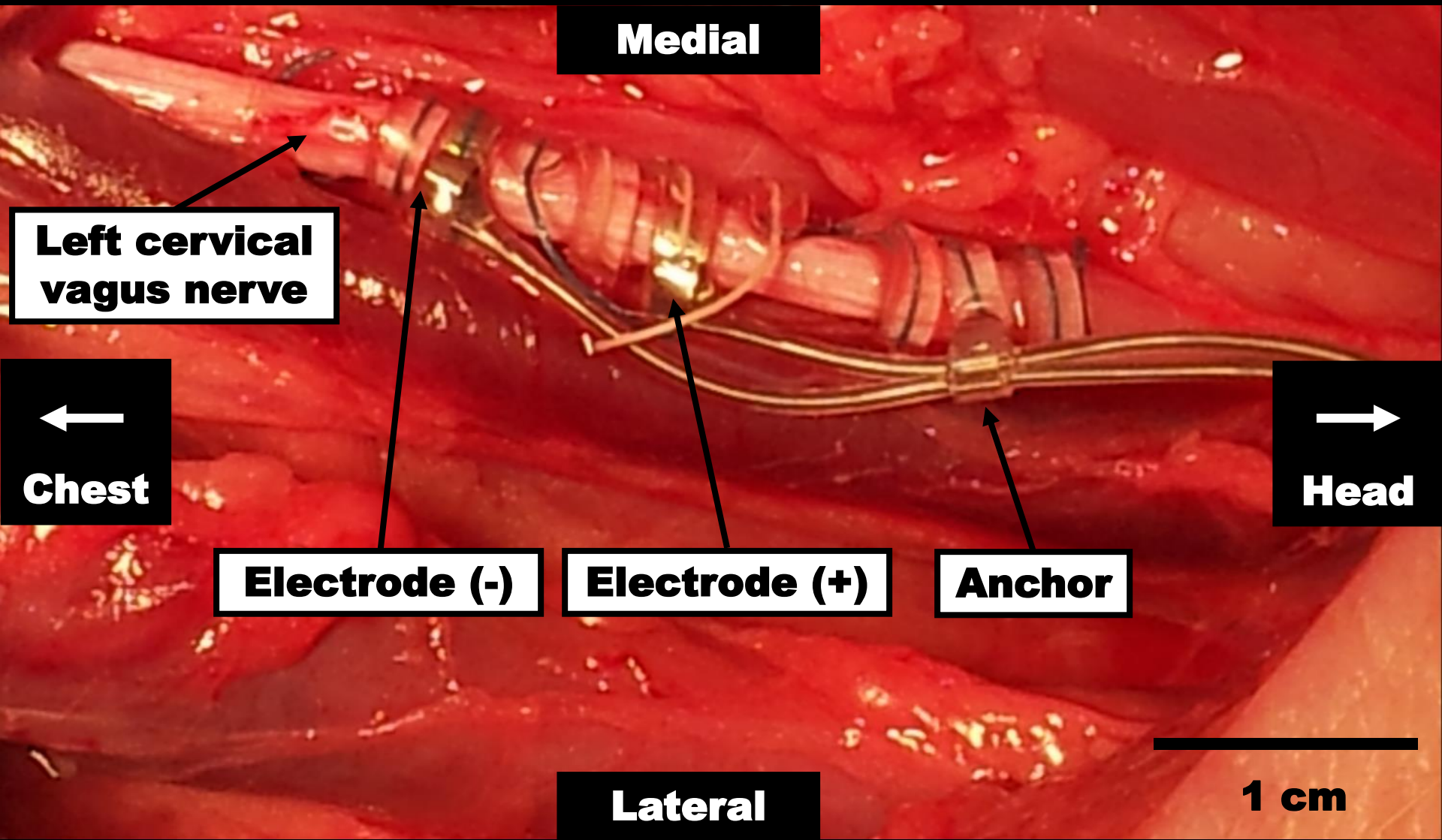



"Rebalanced Autonomic Activity"

# Vagus Nerve Stimulation

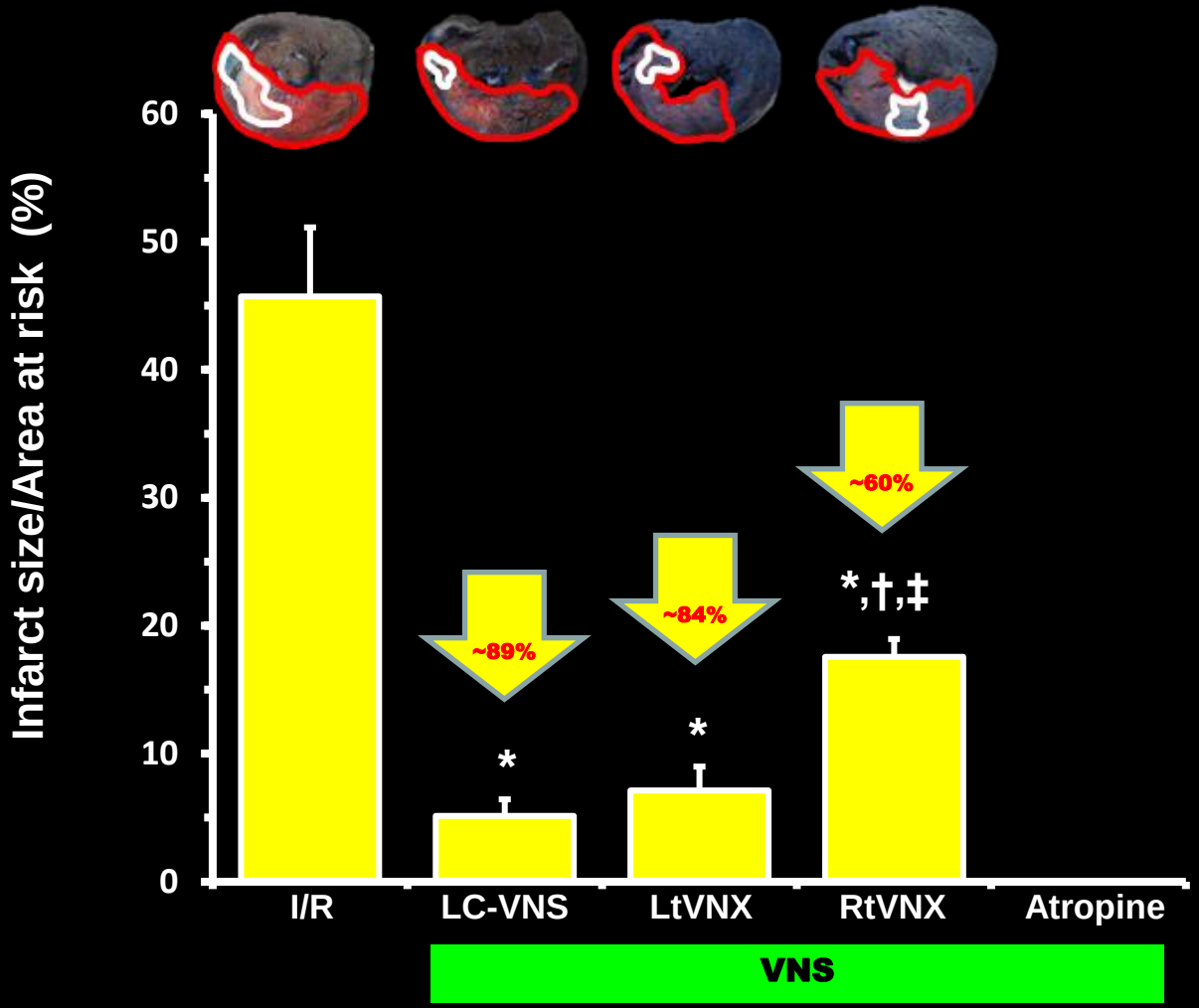


# Electrode Placement on Left Cervical Vagus Nerve



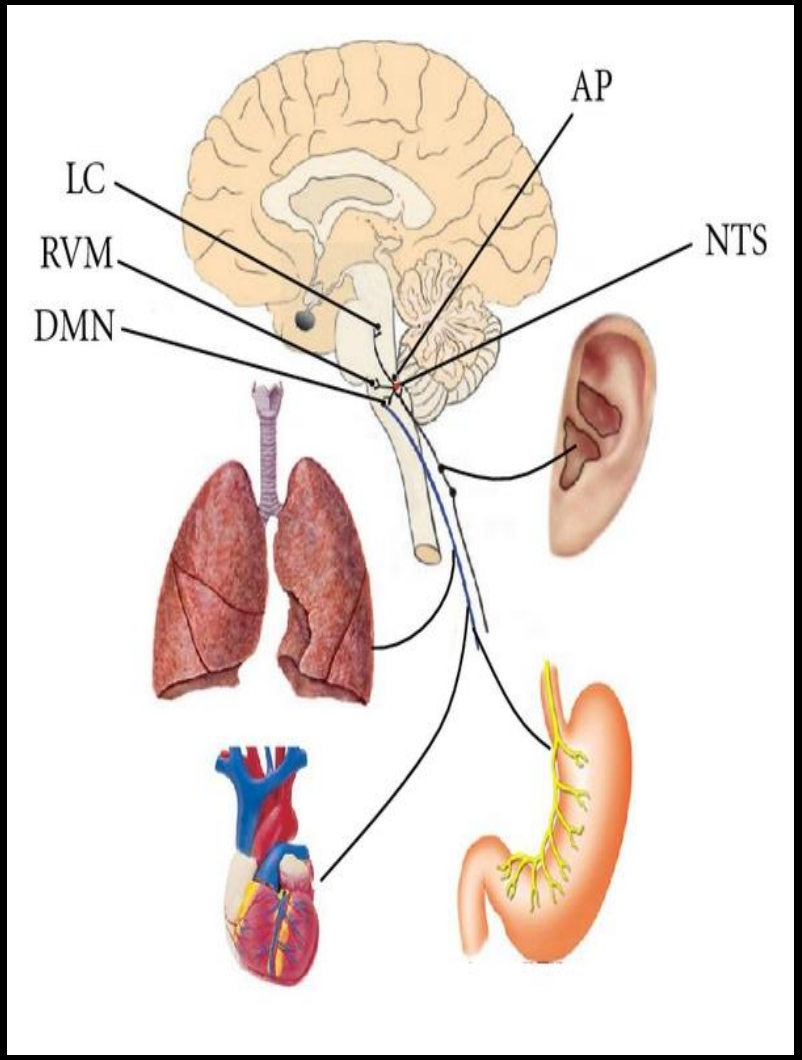
# The Effect of VNS on Infarct Size

# Infarct Size

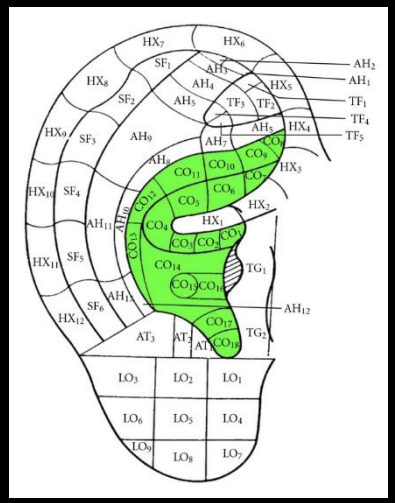



* $P < 0.05$ vs I/R group
† $P < 0.05$ vs LC-VNS group
‡ $P < 0.05$ vs LtVNX group

# Future Directions for Clinical Application







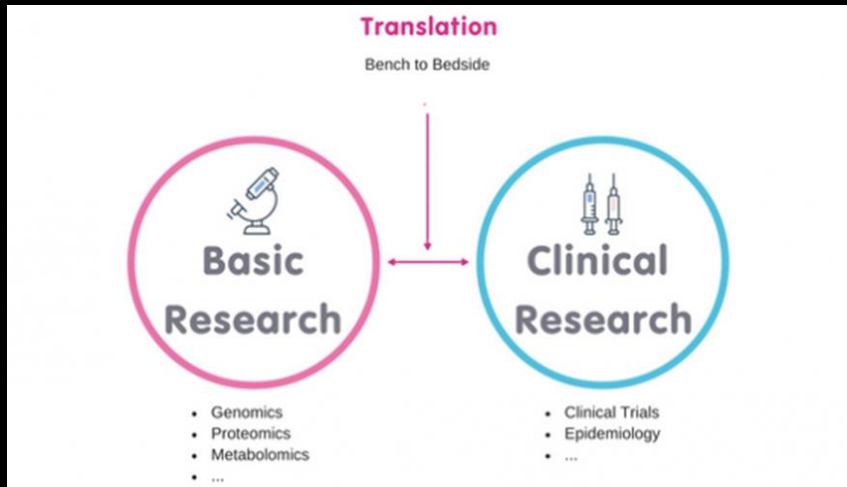
# Conclusions

- Translational research is critical to the evolution of biomedical research and practice in the 21st century.

- The key problems that led to its emergence remain a challenge.
  - The relatively long time from discovery to use and impact
  - The relative low proportion of discoveries that survive that journey

# Conclusions

- Requires different disciplines to work together
- Goes against traditional academic medicine culture
- Requires team-oriented people, not individualists



# “Persistence is bitter , but its fruit is sweet”


# Thank you for your kind attention

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