

“Do You Like Asking Questions?  
Do You Like Helping People?  
Have you Considered **Toxicology**?!”

2018 SOT Undergraduate Diversity Program

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JLC-Biomedical/Biotechnology Research Institute

**North Carolina Central University**

Department of Pharmacology, Curriculum in Toxicology

**University of North Carolina-Chapel Hill**

March 10, 2018

**What Do You See?**

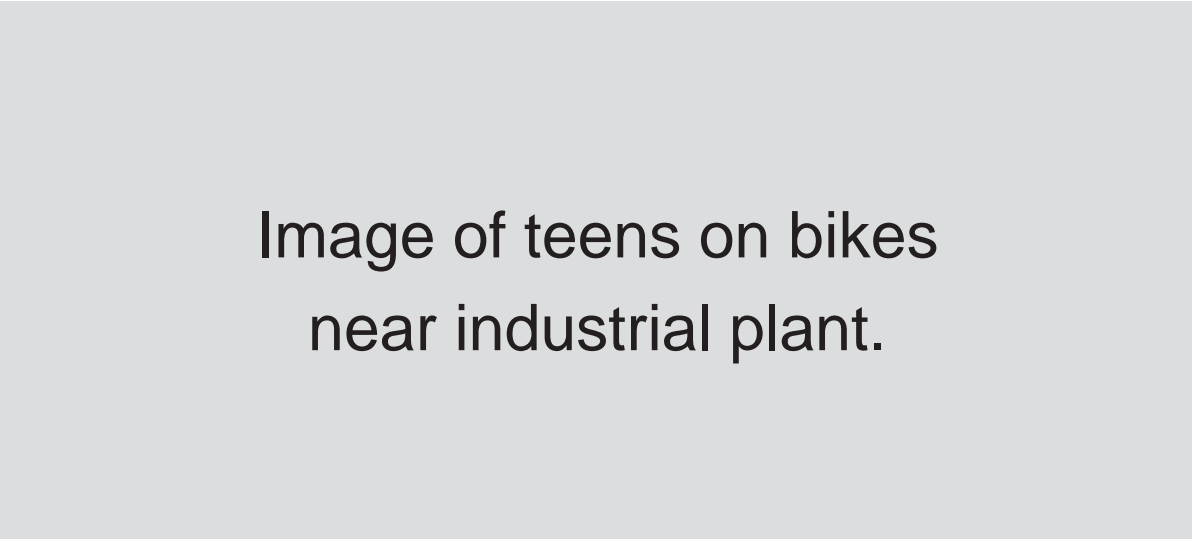


Image of teens on bikes  
near industrial plant.

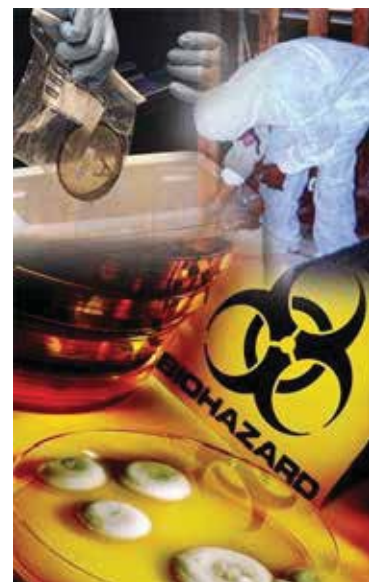
## More Than \_\_\_ Sites Released Hazardous Pollutants Due to Hurricane Harvey in Houston



[https://commons.wikimedia.org/wiki/File:Houston\\_Ship\\_Channel.jpg](https://commons.wikimedia.org/wiki/File:Houston_Ship_Channel.jpg)

## What is Toxicology?

- The traditional definition of toxicology is "the science of poisons."
- A more descriptive definition of toxicology is "*the study of the adverse effects of chemicals or physical agents on living organisms.*"



# Hey, We're Family!



## Society of Toxicology

1101 FOURTEENTH STREET, N.W., SUITE 1100, WASHINGTON, D.C. 20005-5601  
Tel: (202) 371-1393 FAX: (202) 371-1090

December 15, 1992

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Mr. Antonio Baines  
c/o Dr. Maxwell A. Bempong  
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Norfolk State University  
2401 Corprew Avenue  
Norfolk VA 23504

Dear Mr. Baines:

Congratulations! You have been selected to receive a Minority Student Travel Award for the 1993 Annual Meeting of the Society of Toxicology, March 14-18 in New Orleans, Louisiana. This travel grant was generously funded by the National Institutes of Health and the R.W. Johnson Pharmaceutical Research Foundation.

The Society of Toxicology will make your travel arrangements to and from the meeting and provide you a sleeping room for the evenings of the 13th, 14th and 15th (roommates will be assigned). In addition, a modest stipend will be sent to you prior to the meeting to cover your home city airport transfers and other incidentals. In order to complete our travel arrangements, we ask that you complete and return the enclosed acceptance form by **January 8, 1993**. Further details of the meeting (the preliminary program) will be sent to you sometime this month.

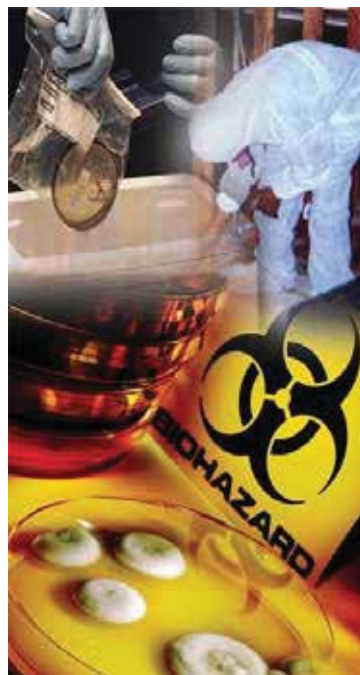
You will be met at the New Orleans airport Saturday, March 13 and given instructions about transportation to the Doubletree Hotel.

## My Education/Career Path to Toxicology

- BS in Biology from Norfolk State University (4 years)
- PhD in Pharmacology and Toxicology from the University of Arizona (5.5 years)
- Postdoctoral fellowship in Pharmacology at UNC-Chapel Hill (5 years)
- College professor, cancer biologist, toxicologist in academia at North Carolina Central University (11 years)

# Pop Quiz: What is Toxicology?

How is toxicology  
involved in our everyday  
lives?



## Chemicals are Ubiquitously Present in Our Environment

- Chemicals are natural, biological, or synthetic in origin
  - Natural (food, metals, minerals)
  - Biological (toxins from bacteria)
  - Synthetic (manufactured through chemical processes)
- Approximately **100,000** chemicals are currently in use worldwide
- About **500** new formulations enter the marketplace annually



# Do You Want to Smoke? Is This Safe?



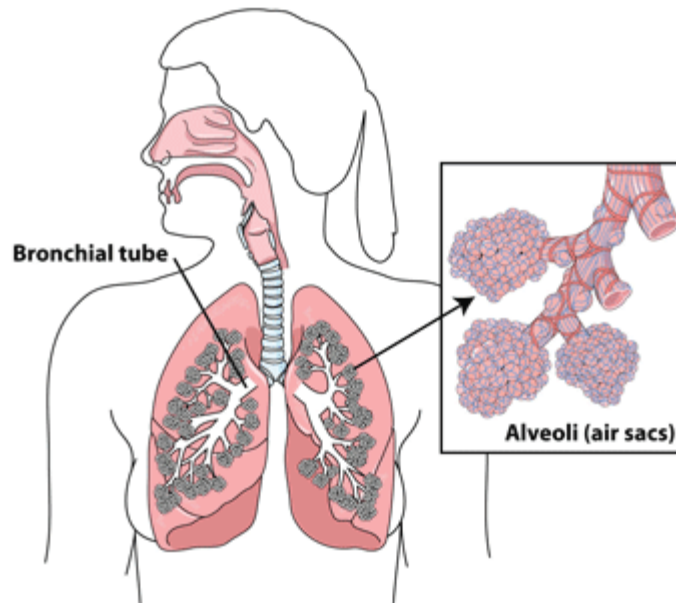
[https://upload.wikimedia.org/wikipedia/commons/thumb/6/68/E-Cigarette-Electronic\\_Cigarette-E-Cigs-E-Liquid-Vaping-Cloud](https://upload.wikimedia.org/wikipedia/commons/thumb/6/68/E-Cigarette-Electronic_Cigarette-E-Cigs-E-Liquid-Vaping-Cloud)

## Concerns with Electronic Cigarettes

- Studies performed on e-cigarette vapor have detected 31 potentially harmful chemicals (ex. nicotine, formaldehyde, acrolein, etc.)
- E-cigarettes are linked to acute respiratory diseases, such as asthma and bronchitis
- Up to 40 percent of particles emitted by an e-cigarette can be deposited in the deepest area of a youth's lungs

Sleiman, M., et al., *Environ. Sci. Technol.*, 2016, 50 (17), pp 9644–9651  
Thornburg, J., et al., (March 2015). RTI Press Publication No. RB-0008-1503

## Deepest Area of the Lungs: Alveolar Region



<https://www.womenshealth.gov/a-z-topics/lung-disease>

## The Key Concept in Toxicology is DOSE



*Father of Modern Toxicology*  
**PARACELSUS—1564**

***“All things are poisonous, only the  
dose makes it non-poisonous.”***

*(Dose alone determines toxicity)*

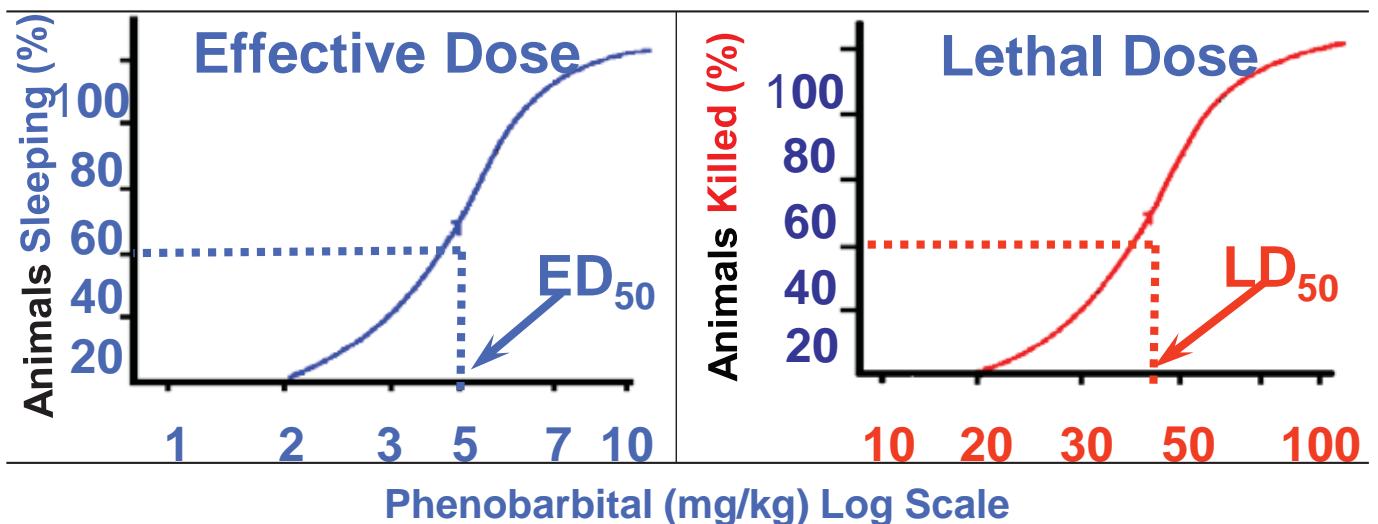
# Beneficial Versus Toxic Effects: It's All About Dose!

Substance	Non-Toxic or Beneficial Dose	Toxic Dose	Lethal Dose
<b>Alcohol</b> <i>ETHANOL BLOOD LEVELS</i>	0.05 %	0.1 %	0.5 %
<b>Carbon Monoxide</b> <i>% HEMOGLOBIN BOUND</i>	< 10 %	20 - 30 %	> 60 %
<b>Secobarbital</b> ( <i>sleep aid</i> ) <i>BLOOD LEVELS</i>	0.1 mg/dL	0.7 mg/dL	> 1 mg/dL
<b>Aspirin</b>	0.65 gm <i>(2 tablets)</i>	9.75 gm <i>(30 tablets)</i>	34 gm <i>(105 tablets)</i>
<b>Ibuprofen</b> <i>E.G., ADVIL &amp; MOTRIN</i>	400 mg <i>(2 tablets)</i>	1,400 mg <i>(7 tablets)</i>	12,000 mg <i>(60 tablets)</i>

**Principles of Clinical Toxicology** (T. Gossel and J. Bricker, eds)

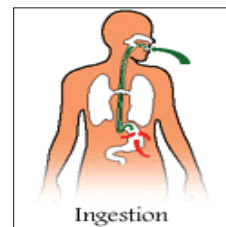
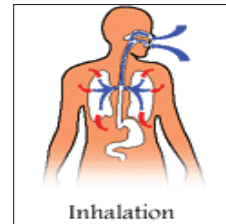
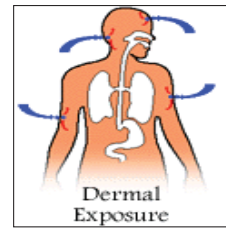
## Dose-Response Relationship

*“The dose makes the difference between a beneficial and a toxic effect”*



# Routes of Exposure

- The **route** (site) of exposure is an important determinant of the internal dose, magnitude of toxicity and the organs and tissues affected
- Different routes may result in different rates of absorption:
  - Dermal (skin)
  - Inhalation (lung)
  - Oral ingestion (Gastrointestinal)
  - Injection
- Toxic effects may be local or systemic



## An Example of Dose and Exposure



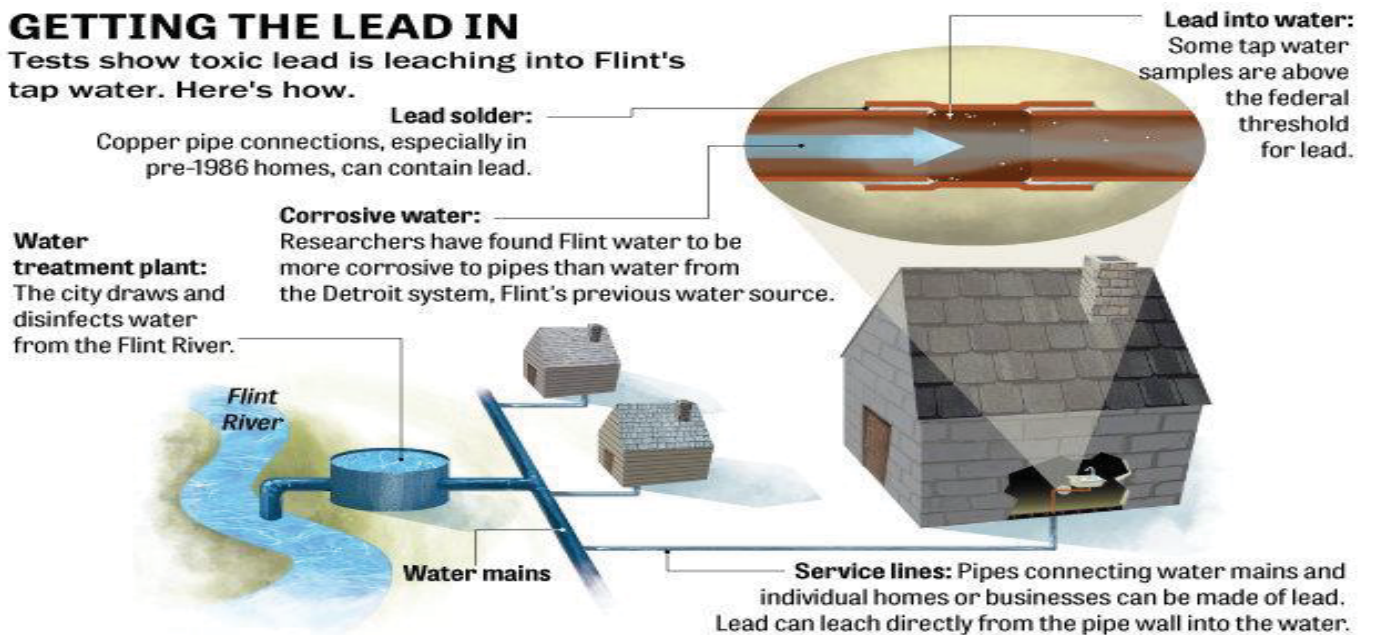
Fall 2015: Lead levels found higher than the acceptable EPA limit of 15 ppb - ranged from 25 ppb and higher, several exceeded 100 ppb



# What Led to the High Lead Levels?

## GETTING THE LEAD IN

Tests show toxic lead is leaching into Flint's tap water. Here's how.



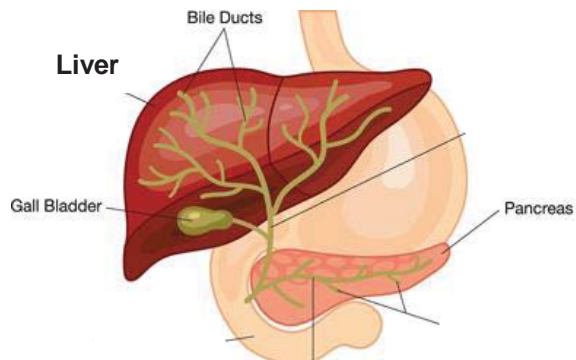
## Guess How Many US Cities Have Lead Contamination Just As Flint, MI?



[https://upload.wikimedia.org/wikipedia/commons/thumb/8/81/Rust\\_from\\_bathtub\\_in\\_Kyiv.jpg/640px-Rust\\_from\\_bathtub\\_in\\_Kyiv.jpg](https://upload.wikimedia.org/wikipedia/commons/thumb/8/81/Rust_from_bathtub_in_Kyiv.jpg/640px-Rust_from_bathtub_in_Kyiv.jpg)

# Biotransformation

- Major mechanism for terminating the biological activity of chemicals
- Occurs in the liver, kidney, lung, and gastrointestinal tract



**The LIVER is the primary site of metabolism**

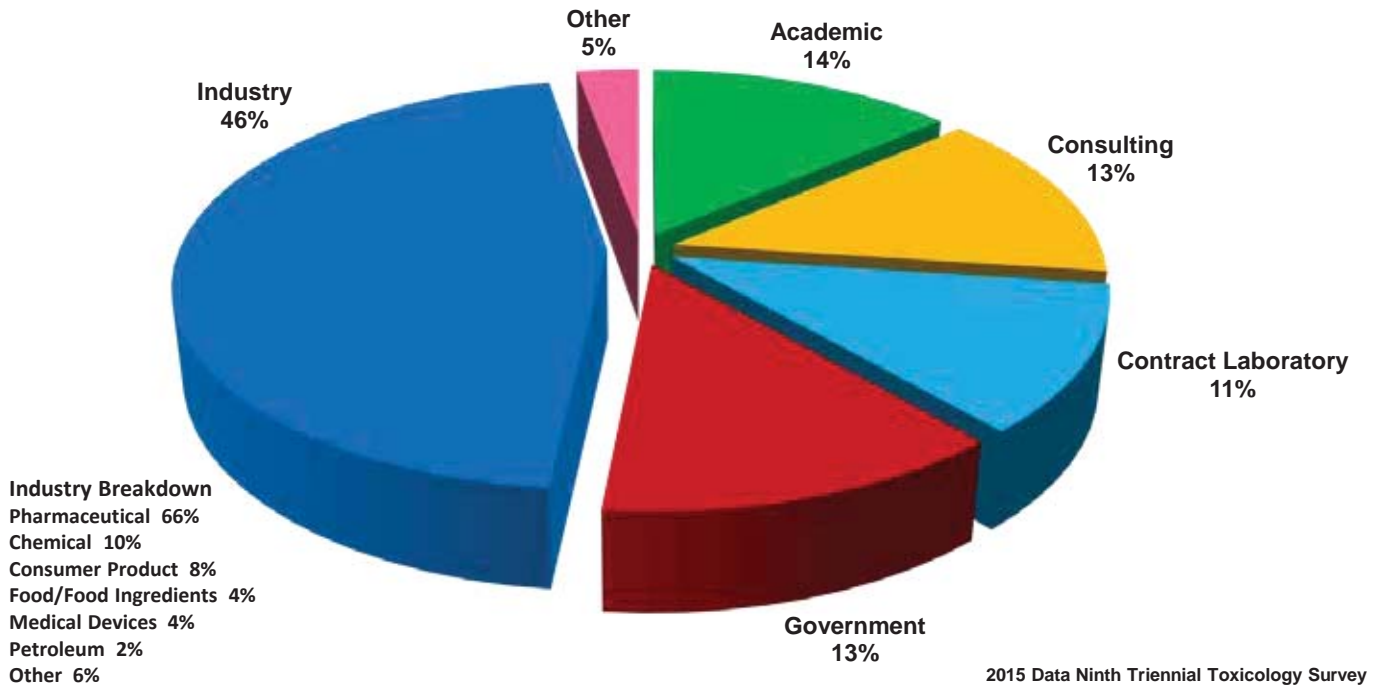
<https://www.niddk.nih.gov/health-information/diagnostic-tests/endoscopic-retrograde-cholangiopancreatography>

## What Does a Toxicologist Do?

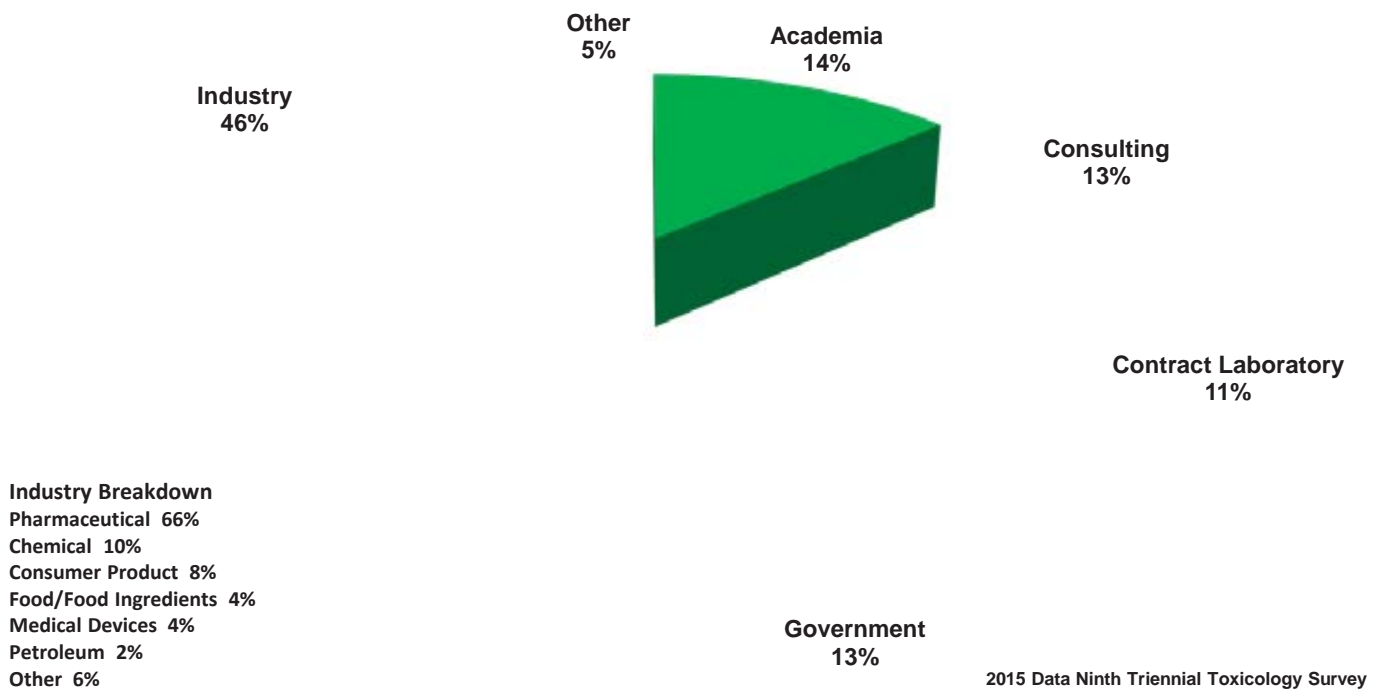
- Develop mechanistic understanding of effects of toxicants
- Ensure safer chemical products
- Develop safer drugs & medicines
- Determine risks from chemical exposures
- Develop treatments for chemical exposures
- Ensure a safe food and water supply
- Forensics



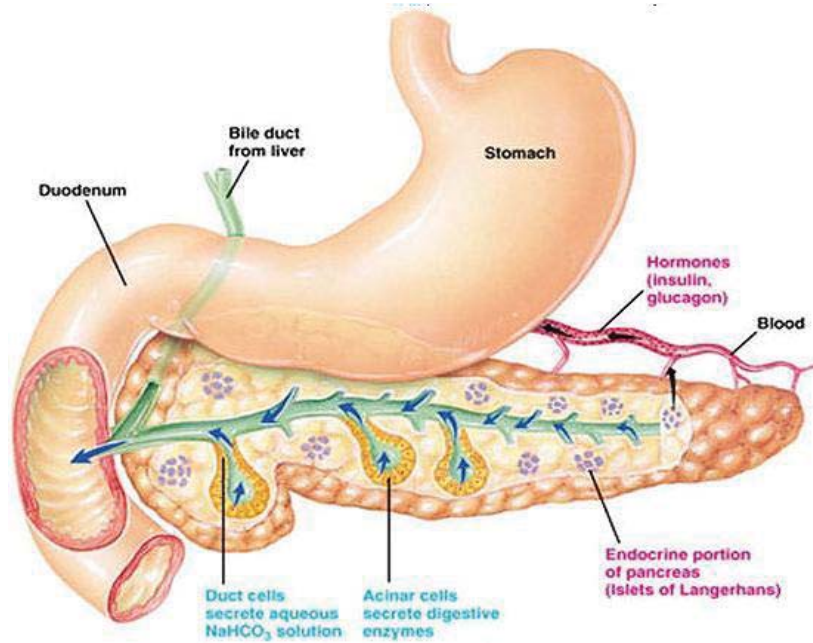
# Toxicology Employment by Sector



# Toxicology Employment by Sector



# What Are the Functions of the Pancreas?



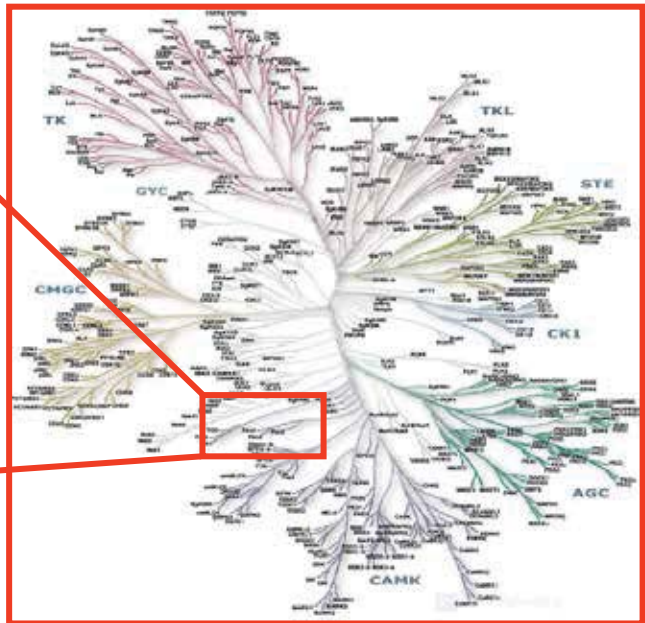
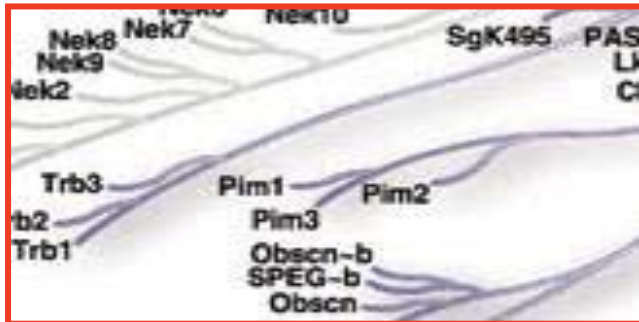
[www.olivelab.org/the-pancreas-overview.html](http://www.olivelab.org/the-pancreas-overview.html)

## Major Concerns of Pancreatic Cancer

- **The 5-year survival rate is 9%, lowest of all major cancers**
- Most patients are diagnosed at an advanced stage
- Most pancreatic cancers are resistant to chemotherapy and radiotherapy
- Survival rates have not significantly changed in the past 40 years

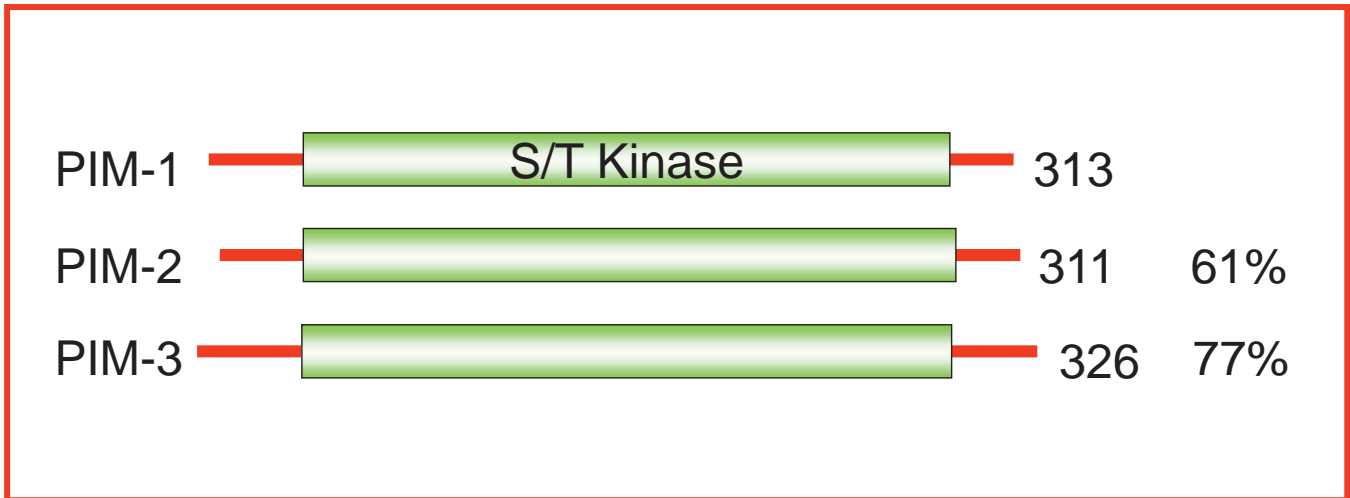
# Human PIM Kinase Family

Human kinome (518)



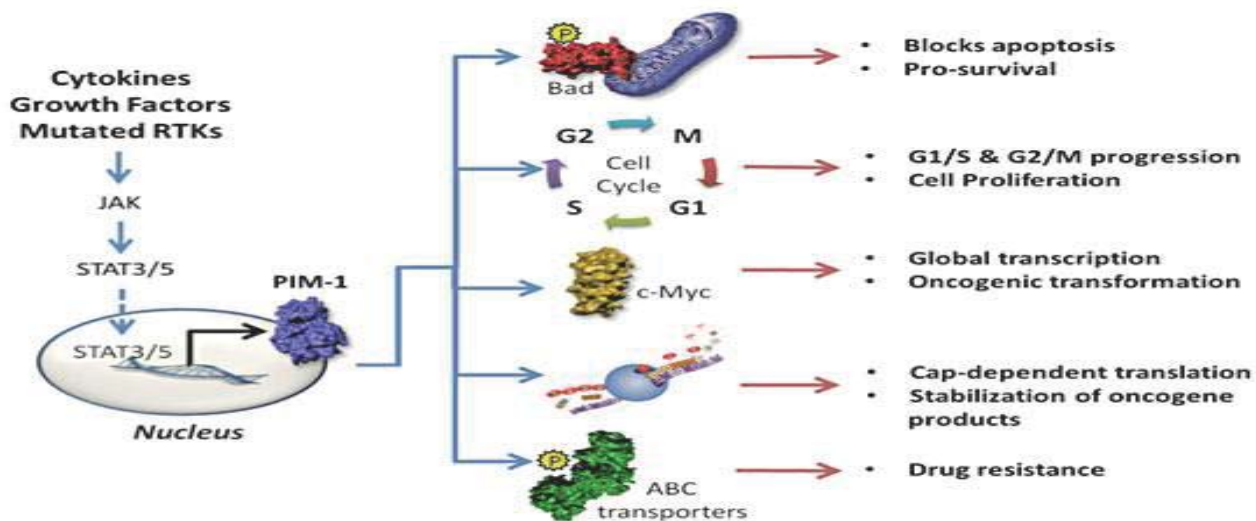
Proviral integration site for the **Moloney murine (PIM) leukemia virus**

# Human PIM Kinase Family



Proviral integration site for the **Moloney murine (PIM) leukemia virus**

# Roles of PIM Kinase Cell Signaling in Cancer

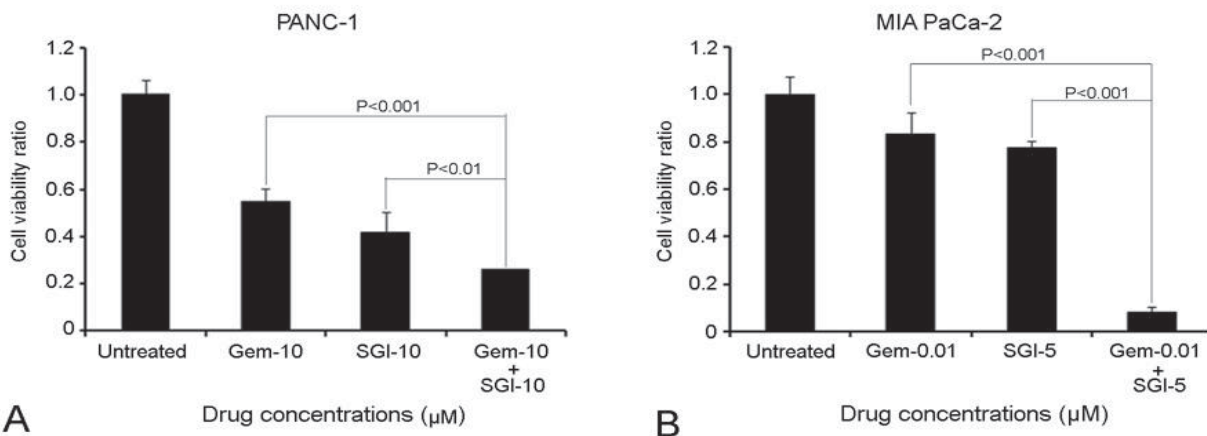


<http://www.toleropharma.com/TP-3654.html>

## Discovery and Development Programs

Lead Discovery	Lead to Candidate	IND Enabling Studies
MP-470 Tyrosine Kinase Inhibitor (c-Met)		
MP-529 Aurora Kinase Inhibitor		
MP-371 Multi-targeted Tyrosine Kinase Inhibitor		
Polo-Like Kinase Inhibitor		
Pim-1 Kinase Inhibitor		
Axl Kinase Inhibitor		
DNMT-1 Inhibitor		
Novel Protease Inhibitor		
JAK2 Inhibitor		
Eg5 Kinesin Inhibitor		
MDM2 Inhibitor		

# The Combination of SGI-1776 (PIM Inhibitor) and Gemcitabine Decreases Cell Viability in PDAC Cells



Xu, D., Baines, A.T. et al., Cancer Biology & Therapy (2013), vol. 14(6), pp. 492-501.

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**SOT** | Society of  
Toxicology

**We Want  
YOU!**