



Disease Diagnostic INventors Challenge – Dec 20, 2018

Following is a summary of the opportunities identified in the recent DDIN Challenge held at the IU School of Medicine in Indianapolis.

Teams of researchers will be invited to submit proposals addressing any of these challenges through a letter of intent process. Selected groups will present an overview of their proposals at a follow-up DDIN event in the April-May 2019 timeframe with an opportunity to win up to \$30,000 in seed funding – stay tuned for more details.

1) **Improved Diagnosis of Early Stage Damage of Pancreatic Beta Cells in Type I Diabetes**

Type I diabetes is characterized by decreasing function and eventually death of insulin producing beta cells. [Raghu Mirmira](#) described how improved biomarkers of early phase damage and death of beta cells may be helpful for guiding early intervention in patients on the pathway to Phase I diabetes. A recent review of beta cell biology can be found [here](#). Raghu has found that some epigenetic markers – e.g. specifically methylated DNA – are linked to beta cells. A recent review of beta cell potential biomarkers can be found [here](#). The slides presented by Raghu can be found [here](#).

2) **Rapid Differentiation of The Good, The Bad and The Ugly**

[Naga Chalasani](#) overviewed 4 areas of need where rapid tests are needed to quickly differentiate patient samples. A link to Naga's slides can be found [here](#). In all four cases, both normal and abnormal patient samples are available. Areas of need include:

- a) Hepatorenal syndrome A blood based test that could accurately diagnose the onset of hepatorenal syndrome would be highly desirable
- b) Improved early detection of Barrett's Esophagus and similar dysplastic conditions of the esophagus. Barrett's esophagus is a condition where patches of dysplastic growth of cells lining the esophagus are readily identified by visual contrast with normal cells. Similar dysplastic conditions are more difficult to detect visually. Improved techniques for rapid visualization or identification of abnormal patches of dysplastic growth in the esophagus are needed, perhaps using hyperspectral imaging or the use of fluorescence, near IR, Raman or other types of imaging or through the use of rapid chemical imaging of biomarkers indicative of normal and abnormal cells.
- c) Improved rapid differentiation of hyperplastic and non-hyperplastic polyps from colonoscopy. Colonoscopy is a very common procedure, but the delay in time between removal of polyps in the procedure and diagnosis of hyperplasia is too long (about a week). New techniques are needed that enable immediate differentiation of normal and abnormal polyps, perhaps even allowing in situ measurement during the colonoscopy procedure. Collections of normal and abnormal samples are available for testing of either imaging approaches or for typing based on the detection of chemical biomarkers.
- d) Improved detection of pancreatic cysts with diagnosis of likelihood of progression to pancreatic cancer. Multiple samples are available showing progression over time. An improved diagnostic for early detection is needed.

3) **Rapid Identification of Margins During Surgery**

[Leonidas Koniaris](#) described the need for improved tools to define margins during surgery, where current techniques often result in a combination of overaggressive removal of healthy tissue and an unacceptable failure rate in leaving behind pieces of tumors, etc. Recent work on medical diagnostics to improve outcomes include fluorescent reagents for enhancing margin boundaries ([link](#) and [link](#)) or the work of Graham Cooks at Purdue on the development of MS tools to improve differentiation ([link](#) and [link](#)). Additional imaging, spectroscopic or chemical analysis techniques are needed to simplify and streamline the accurate assessment of margins in surgery and improve patient outcomes. [Link](#) to slide deck.

4) **Improved Biomarkers for COPD**

[Matthias Clauss](#) described the development of a new antibody-based therapeutic targeting Emap II for treating COPD, and the need for a companion diagnostic that would be predictive of patient response. [Link](#) to slide deck.

5) **Companion Diagnostics for Gene Therapy Treatments for Hemophilia**

[Roland Herzog](#) described current progress in the development of AAV-mediated gene therapy treatments for hemophilia and the need for companion diagnostics to facilitate treatments and improve patient outcomes. One of the most significant side effects of treatment can be an immune response to the clotting factor (factor 8 or 9) produced in AAV-transfected liver cells. An assay that would provide very early warning of the very beginning of an immune response to this clotting factor might allow treatments that would prevent full-blown immunity and failure. [Link](#) to slide deck.

6) **Improved Diagnostics for Treating Wound Biofilms**

[Chandan Sen](#) described recent studies of wound biofilms and wound metabolomics and the need for point of care/wearable diagnostics capable of measuring several small molecule secondary metabolites that are characteristic of bacteria within biofilms. Slides can be found [here](#)

7) **In Situ Measurement of pH, Ca⁺⁺ and F⁻ at tooth surface**

[Simone Duarte](#) made an *ad hoc* presentation on the need for *in situ* measurement of pH, fluoride ion and calcium ion at tooth surfaces underneath dental plaques. A nondestructive testing method that can be performed in place and repeatedly over time to allow kinetic profiling is needed. While color or fluorescence-forming reagents are available for each of these analytes, getting the reagents to the tooth surface underneath the biofilm presents significant challenges.

Other presentations: In addition to these challenges, several other presentations were made.

Highlighting Genomics and Data Science capabilities of IUSM

[Yunlong Liu](#) and [Kun Huang](#) presented an overview of the capabilities of IUSM's [Laboratory for Computational Genomics](#). The group has an outstanding collection of Illumina, Oxford and other



sequencers and is the most powerful sequencing lab for medical genomics in the Midwest. They have the capacity to do 200 full genomes per week, and also have outstanding capabilities for RNA seq, single cell analytics (RNA, ATAC, CNV, protein), CytoF, Qiagen RNA/DNA extraction from blood as well as computational/modeling/data visualization related to these studies. Groups requiring these capabilities are invited to reach out to Yunlong and Kun to learn more. [Link](#) to slide deck.

Updates from Previous Winners

Short progress reports were presented by three winning teams awarded in Summer 2018.

- Supersoakers – Device for rapid diagnosis of acute kidney failure – slides [here](#)
- CPR Team – Device for rapid assessment of bacterial susceptibility to antibiotics – slides [here](#)
- Sierra Club – Sensitive MS-based assay system for detection of pathogenic bacteria – slides [here](#)

Keynote Presentation: Edwin Simcox, CTO, HHS: HHS Vision for Accelerating Innovation in the Prevention, Diagnosis and Treatment of Kidney Diseases

A presentation by Edwin Simcox highlighted the utility of innovation competitions in general, while specifically outlining recent progress in KidneyX, a new HHS initiative aimed at reinventing the current paradigm for kidney dialysis and treatment. New rapid, inexpensive and dependable companion diagnostics to improve diagnosis and treatment are needed, including measurement of biomarkers of kidney function and of therapeutic agents used in treating the condition. \$2.6 MM in prizes are available in two funding phases. First submissions are due Feb 28, 2019. More information can be found at www.kidneyx.org

This is the first of many anticipated HHS innovation competitions. Of line discussions with Edwin suggested that type II diabetes co-morbidities and Lyme disease diagnosis may be the focus of future competitions.



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DISEASE DIAGNOSTICS INVENTORS CHALLENGE

Part 1: Networking Event

Identify compelling clinical needs and opportunities that could be addressed via innovations in measurement science



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Original Vision for the DDI Challenge

What if we could bring together....

Physicians, clinical researchers, biologist and basic life scientists with an understanding of the limitations and opportunities for using measurement technologies in medicine



...and...

Engineers, analytical chemists and measurement science experts skilled in developing assays and creating new analytical instruments

Valuable innovations capable of transforming healthcare

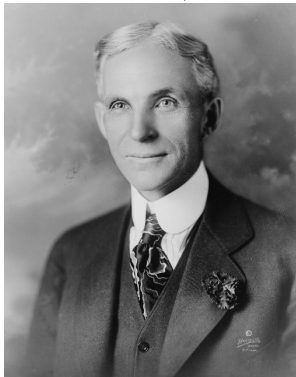


DISEASE DIAGNOSTICS VENTORS CHALLENGE

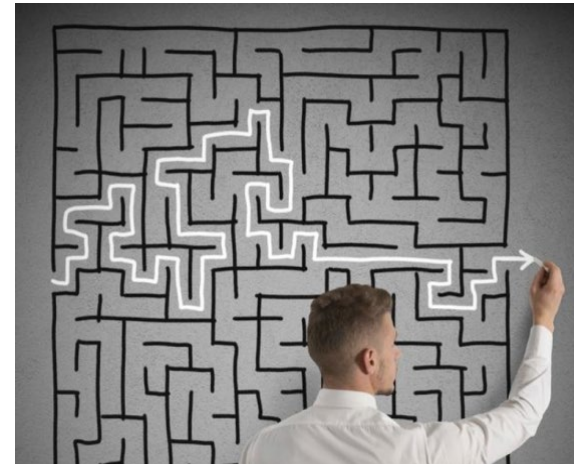


Measurement Science: Key Tool for Problem Solving

“You can’t improve what you can’t measure”



Henry Ford



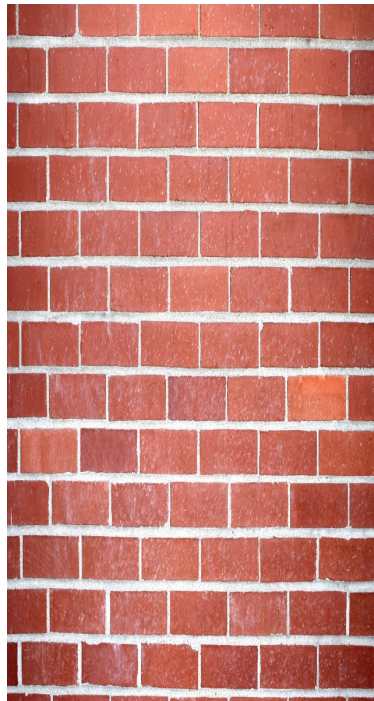
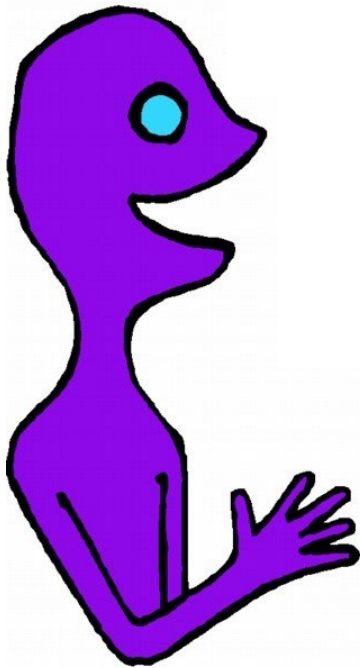
Did You Know...

- IN is a global leader in analytical instrumentation and measurement science?
- We have 7 of the world’s top 100 measurement scientists!!!

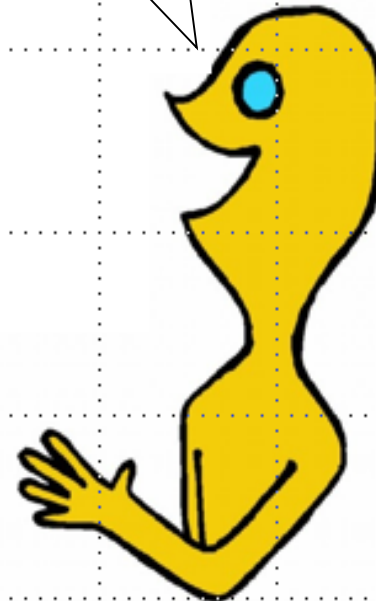


But... connecting these experts with medical and clinical experts can be challenging...

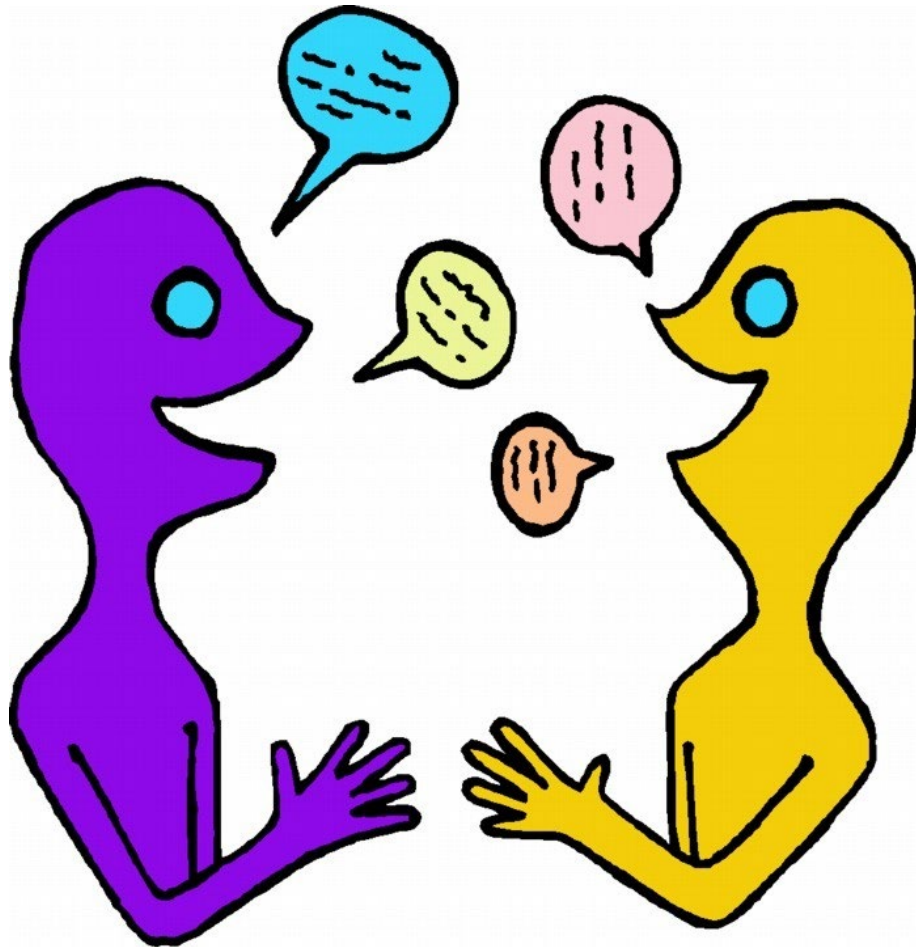
Anybody over there?



Can you hear me now?



Can we enable 'call and response' problem solving by bringing these groups together?



Our Initial Disease Diagnostic INventors Challenge

June 28th & 29th, 2018 at Purdue University

- Two day event
- Good turnout from PU, IUSM, IUB, IBRI and ND
- Fun – high enthusiasm
- Four project teams were selected for seed funding (we will be hearing from them over lunch)

Constructive Feedback

- Span of time was too short - better to separate the ‘call’ (definition of problem or opportunity) from the ‘response’ (proposed solution) so that teams have time to develop
- Hold next ‘call’ at IUSM so that attendance by clinical/medical experts is easier

Disease Diagnostic INventors Challenge 2.0

Dec 20, 2018 at Purdue

Tommy Sors – PI4D creator of DDIN Challenge 1.0, invites others

Chris Welch, ICASE (Indiana Consortium for Analytical Science & Engineering – a joint venture of IU, PU and ND) agrees to help

Mark Geraci – shares relevant experience with successful innovation competitions at U. Colorado, offers to help recruit clinical/medical presenters

Alan Palkawitz, IUSM agrees to help

Indiana CTSI agrees to host in HITS building

(special thanks to Nancy Nysewander and Julie Driscoll)

(special shout out to Melody Warman on her retirement TODAY!)

Introductions

Briefly...

Hello
my name is

Name:

Organization:

Area of Expertise/Interest:

If you are not registered for today's meeting please provide your contact information so we can send a meeting summary and follow up information

Agenda

8:30 AM	Registration and Breakfast
9:00 AM	Welcome and Opening Remarks
9:15 AM	Keynote Presentation - Edwin Simcox, Chief Technology Officer, HHS
<div> <div>Biomedical Needs/Opportunities</div> <div>All I want for Christmas is....</div> </div>	
9:45 AM	Raghu Mirmira
10:05 AM	Naga Chalasani
10:25 AM	Leonidas Koniaris
10:45 AM	Matthias Clauss
11:05 AM	BREAK
11:25 AM	Roland Herzog
11:45 AM	Yunglong Liu & Kun Huang
12:05 PM	Chandan Sen
12:25 PM	Lunch and update from previous INventors Challenge winners
12:25 PM	Supersoakers
12:40 PM	CPR Team
12:55 PM	Sierra Club
1:30 PM	'Speed Dating' and Convergence Assembly
3:00 PM	Conclusion



Keynote Presentation:

Edwin Simcox

Chief Technology Officer

US Department of Health & Human Services



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12:45 PM	Lunch and update from previous INventors Challenge winners
12:45 PM	Supersoakers
1:00 PM	CPR Team
1:15 PM	Sierra Club

Please grab a box lunch out in the hall and return to this room to hear updates.

1:30 PM 'Speed Dating' and Convergence Assembly

3:00 PM Conclusion

11 groups for Networking

- 7 new need/opportunity areas
- 3 previously awarded projects
- 1 'process improvements' (suggest how we can improve the event in future)

Break into small groups – 5 minutes discussion with each team/representative

- Can you yourself help?
- Recommend a colleague from your institution?
- General Advice and Suggestions

When the bell rings, move to the next group

Capture comments and suggestions on flip chart

Short summary from each group at 3:00 pm

Next Steps

- We will summarize the findings from today's event, send to all attendees and make available on a website that is under construction.
- If you didn't register, make sure the organizers have your contact information.
- Please share/report with your colleagues who were unable to attend today.
- We will reconvene in March-April 2019 timeframe to award seed funding to several research proposals that best address one of the needs/opportunities presented today.
- Winning teams will combine clinical as well as measurement science expertise, and ideally will involve researchers from more than one institution.
- Stay tuned for additional details

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And Thanks to You for Attending!
Safe Travels





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KIDNEYX

INNOVATION ACCELERATOR

HHS' Vision for Accelerating Innovation in the
Prevention, Diagnosis and Treatment of Kidney
Diseases

Ed Simcox

*Chief Technology Officer & Acting Chief Information Officer
U.S. Department of Health & Human Services*



Mission

To build an innovation-focused culture at HHS that improves health outcomes and reduces costs



“Working in tandem, the Government and the private sector can promote the nation’s economic growth through innovation”

- Michael Kratsios, Mick Mulvaney
August, 2017

Inter-Agency Innovation Hub

Data

We open data to
fuel internal &
external innovation



Talent

We cultivate talent
through Ignite,
CoLab and EIR



Partnerships

We leverage prize
authority to address
market failures



End-Stage Renal Disease (ESRD)

100,000

Number of Americans
who begin dialysis
every year

\$34.8 billion

Annual Medicare
ESRD budget, or ~1%
of federal budget

40 million

Total number of
Americans living with
kidney diseases

KidneyX.org | @Kidney_X

Mission

Accelerate innovation in the prevention,
diagnosis, and treatment of kidney diseases.

KidneyX Structure

Public-private partnership with the American Society of Nephrology (ASN)

HHS

Market regulator
Research funder
Payer

ASN

Nephrology expertise
Broad network
\$25 million committed

Incentivizing New Products

1. Offer funding opportunities

Series of prize competitions

2. Improve coordination across HHS

Clarify paths to commercialization (FDA, NIH, CMS)

3. De-risk commercialization

Attract outside investment capital

4. Create a sense of urgency

On behalf of people living with kidney diseases

Patient Testimony

*“KidneyX gives me hope
because it’s not going to
reward renal failure”*

Patient Involvement

1. Every prize submission must have patient input
2. Patients are on judging panel
3. Patients are part of KidneyX governance structure

Areas of Focus



Diagnostics

Point-of-care or at home testing kits, real time kidney monitoring



Medications

Drugs designed to treat and slow progression of kidney diseases



Patient Tools

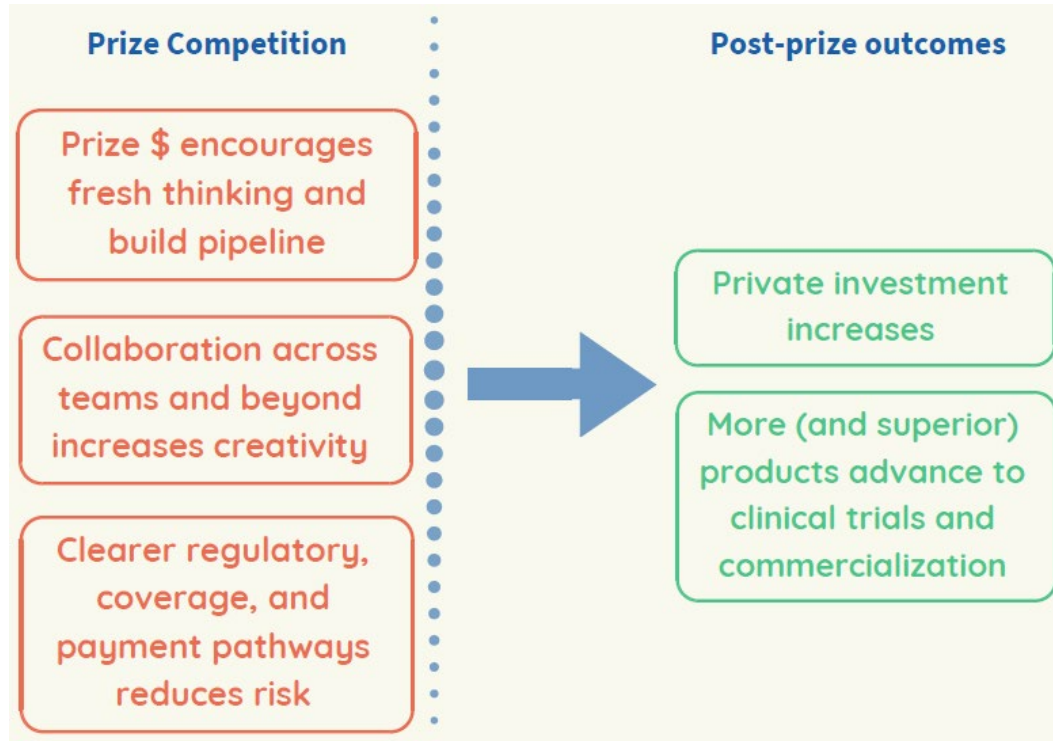
Applications to empower patients to manage kidney diseases (i.e. nutrition app)

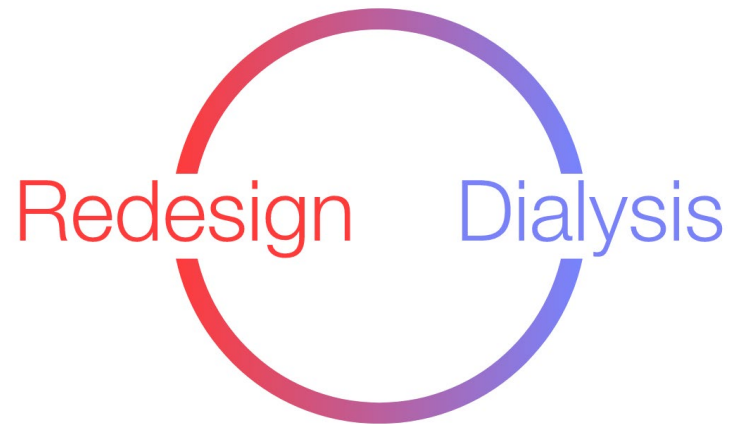


Next-Gen Dialysis

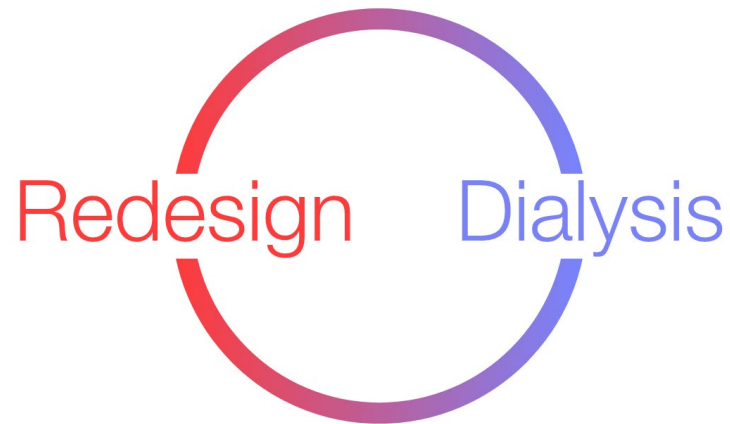
Wearable/implantable dialyzers, vascular access technologies, bio-artificial kidneys

The Power of Prizes





- **\$2.6M** prize available across two phases
- First phase submissions due February 28th, 2019
- First of many prizes to come, your input is needed



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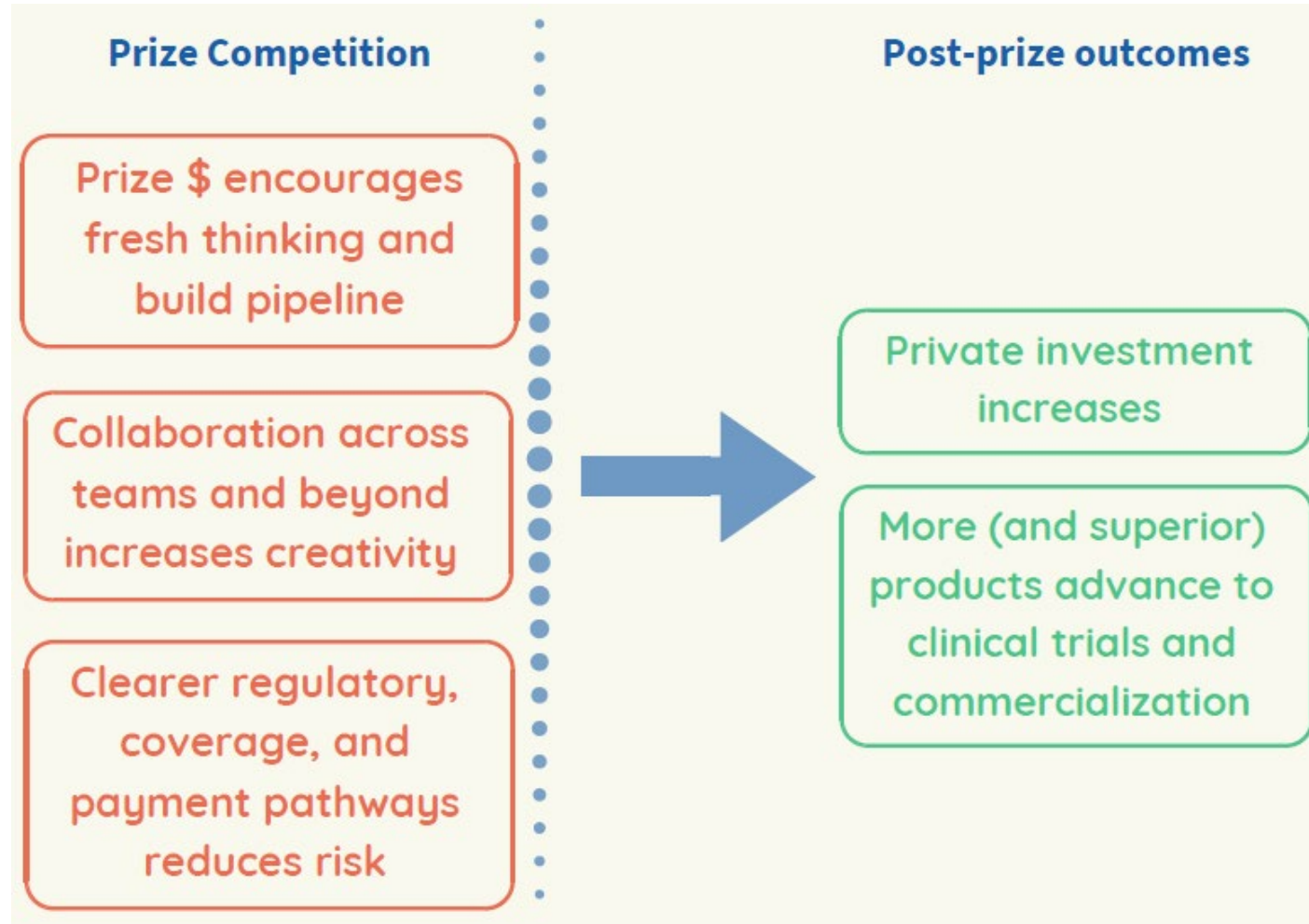
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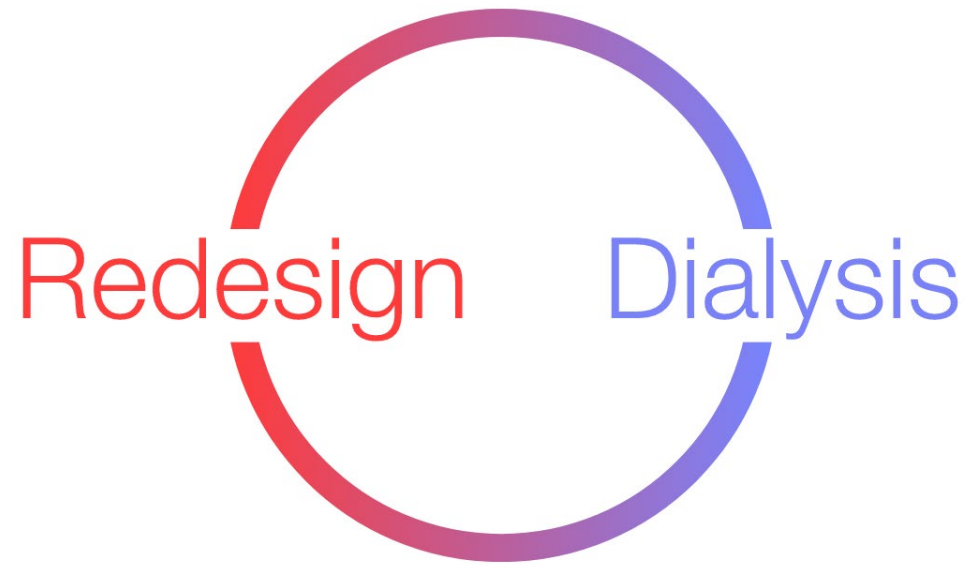


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Biomarkers of β Cell Death and Stress in T1D

Raghu G Mirmira, MD, PhD

Professor of Pediatrics

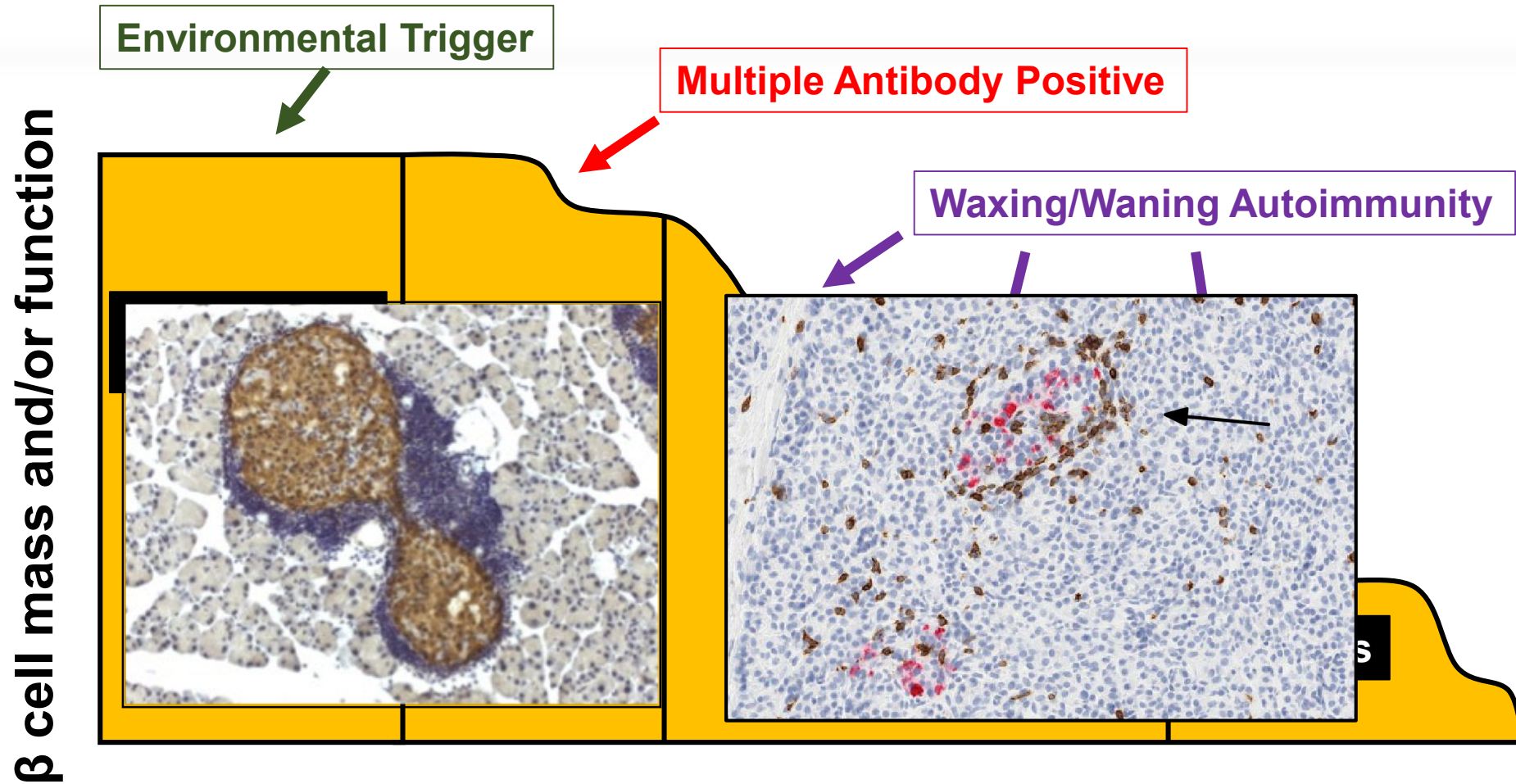
Indiana University School of Medicine



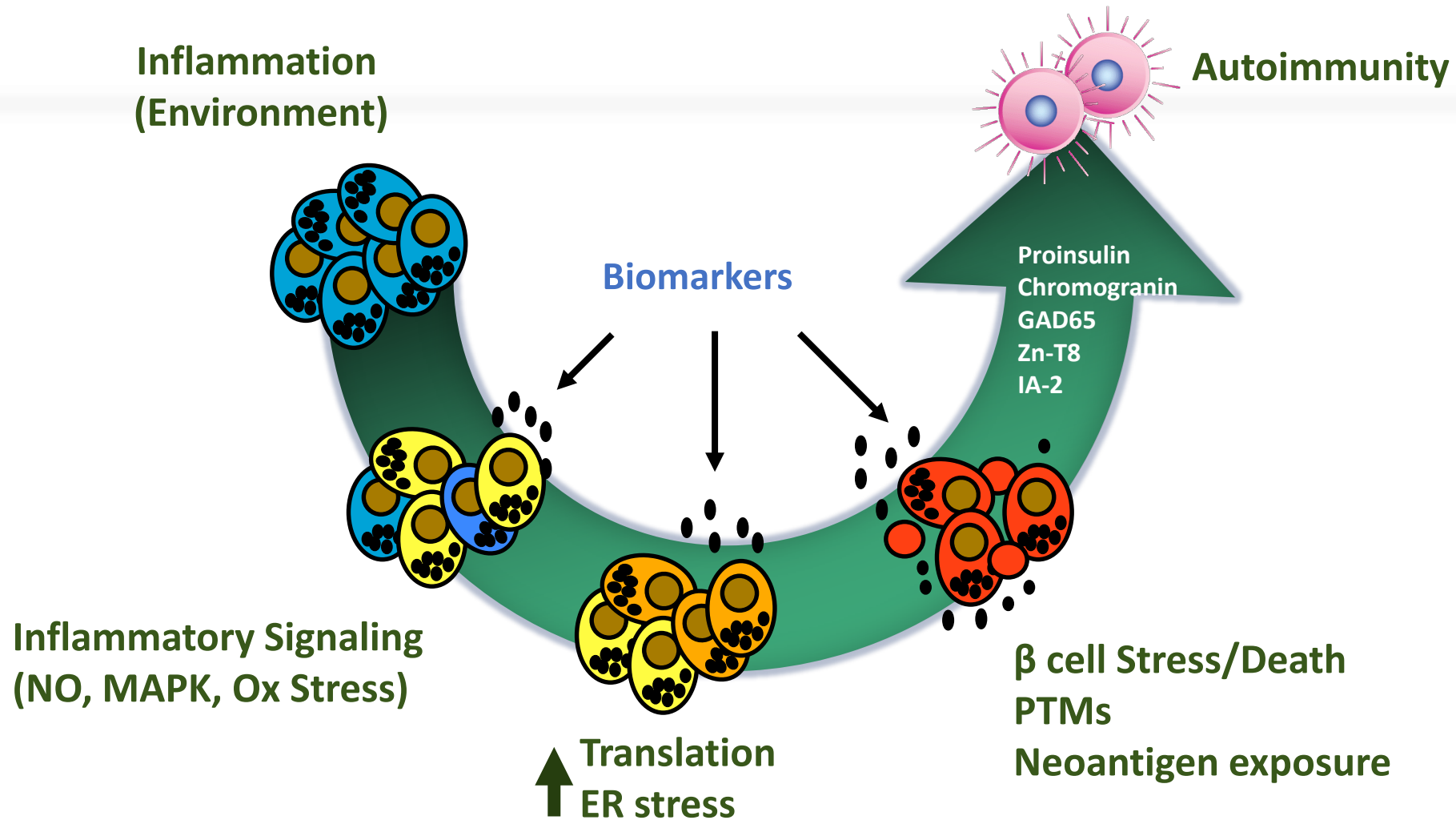
**CENTER FOR DIABETES
AND METABOLIC DISEASES**

INDIANA UNIVERSITY

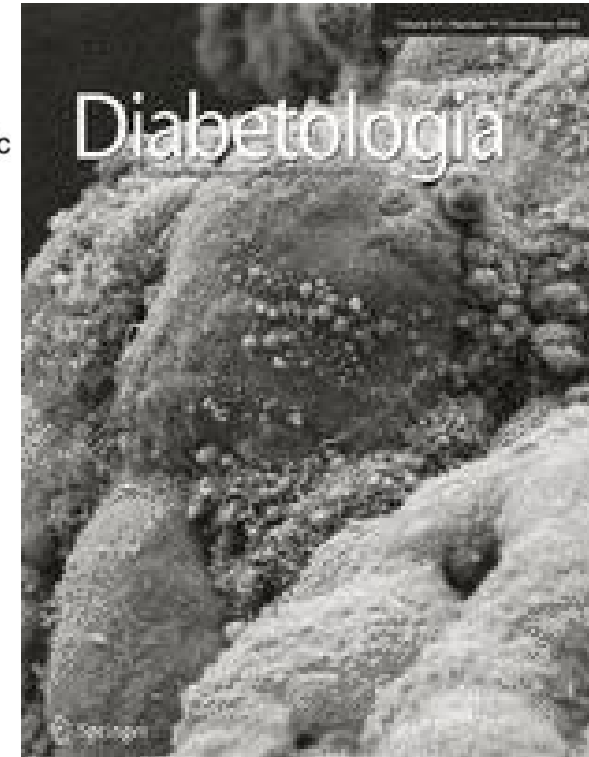
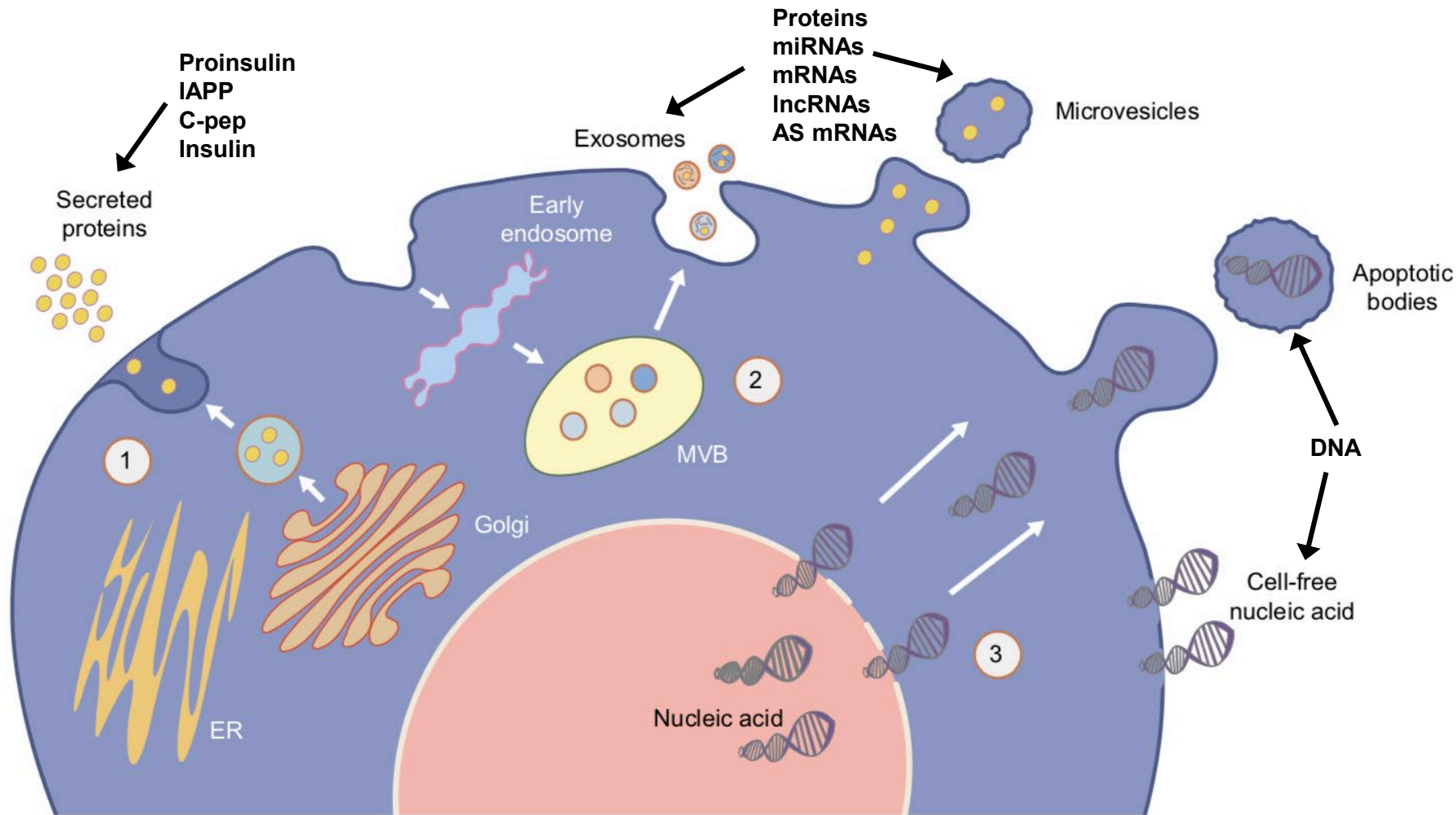
Type 1 Diabetes



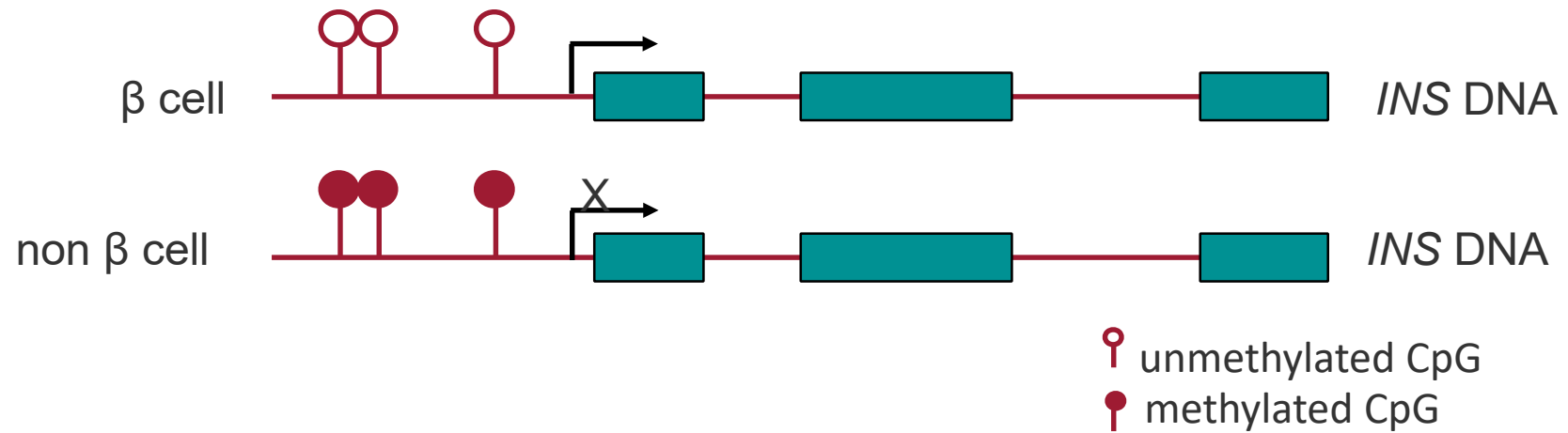
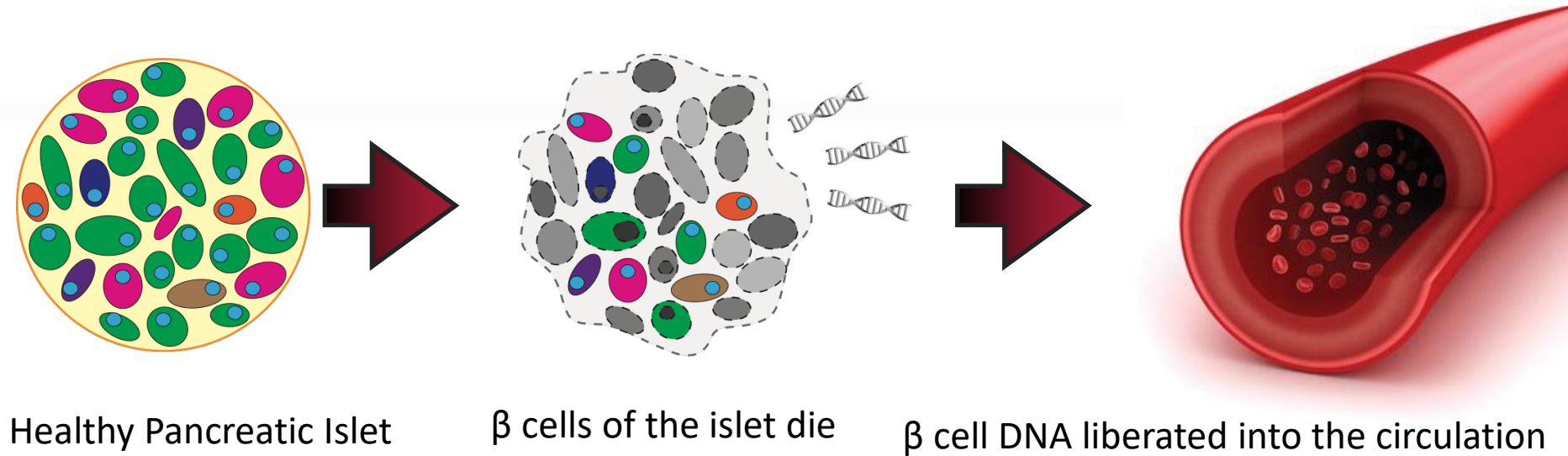
Autoimmunity Develops Late in Type 1 Diabetes Pathogenesis



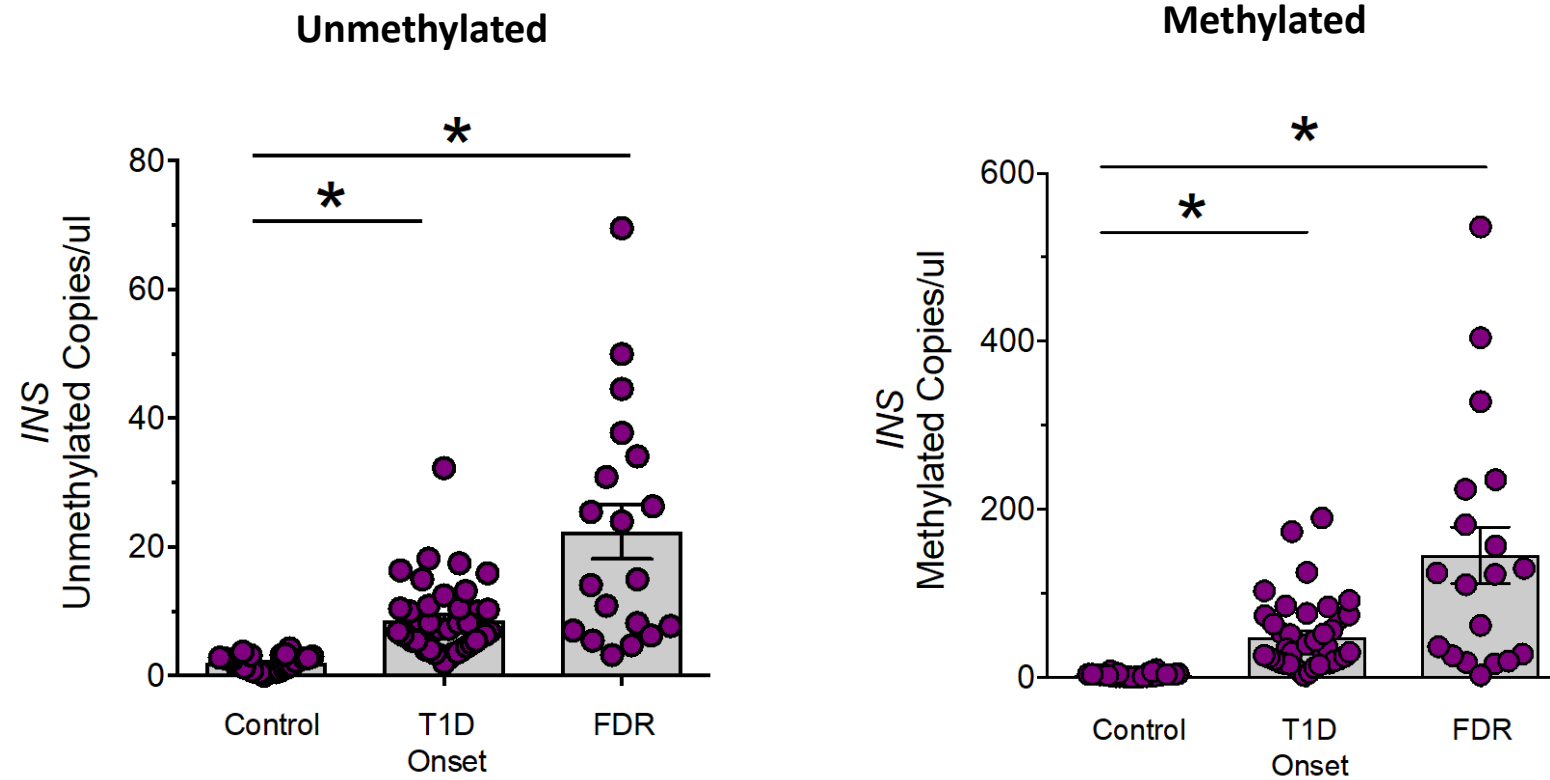
Development of Biomarkers for Identification of Early β -cell Stress in T1D



Epigenetics-based DNA Biomarkers



Utility of *INS*T1D



Selected Gastrointestinal and Liver Disorders

Naga Chalasani, MD

David W Crabb Professor & Associate Dean for
Clinical Research

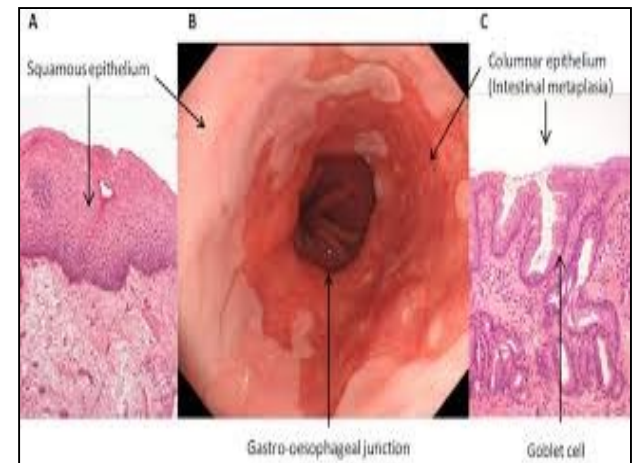
Indiana University School of Medicine
nchalasa@iu.edu

Hepatorenal Syndrome

- A nearly universal complication in individuals with decompensated cirrhosis and ascites
- Oliguria and anuria with progressive worsening of renal function
- Current diagnosis is based on excluding other causes of acute renal failure
- A blood based test that accurately diagnoses hepatorenal syndrome (or impending HRS) would be highly desirable

Dysplasia and cancer in Barrett's esophagus

- Adenocarcinoma of the esophagus is increasing in its incidence – linked to obesity, GERD, and Barrett's esophagus
- Barrett's esophagus can VERY RARELY progress through stages of low to high grade dysplasia and esophageal adenocarcinoma
- Sampling error is a problem
- An imaging diagnostic to identify dysplasia and cancer is an unmet need



Hyperplastic polyps in Colon

- Colonoscopy is the primary modality for CRC screening. Adenomatous polyps are precancerous whereas hyperplastic polyps are not.
- Currently, endoscopists have to remove them and send to pathology to tell which polyps are hyperplastic.
- Imaging based diagnostic for hyperplastic polyps would reduce the expense of polypectomy and pathology.

Pancreatic Cysts

- Pancreatic adenocarcinoma is increasing in its incidence. Due to wide spread use of abdominal imaging, a large number of individuals are detected to have pancreatic cysts.
- Some mucinous types of pancreatic cysts can turn into pancreatic cancer.
- Size and location of the cysts and cyst fluid characteristics can identify patients at risk for pancreatic cancer. Serial imaging is common.
- A blood based diagnostic is highly desirable in risk stratifying pancreatic cysts

Diagnostics Inventors

Challenge

- Catalyze the development of novel disease detection diagnostic technologies
- Surgery focus

Surgical Disease Detection Technologies

What a surgeon does:

- * Maintain or return to normal homeostasis
- * Fix anatomical blocks or leaks to organs and tissues
- * Remove pathological tissues
- * Reconstruct broken mechanisms around movement
- * Cover holes and exposed inner tissues

Areas for diagnostics

- * Pre-operative
- * Intra-operative
- * Post-operative

Areas for diagnostics

Pre-operative

- * Rapid means to determine nutritional status prior to surgery
- * Rapid means to determine pre-existent problems that may cause complications
- * Rapid methods to determine bacterial infections

Areas for diagnostics

Intra-operative

- * Understand margin status during resection
- * Improved understanding of anatomy during procedure
- * Understand when a reconstruction is subpar/problematic

Areas for diagnostics

Post-operative

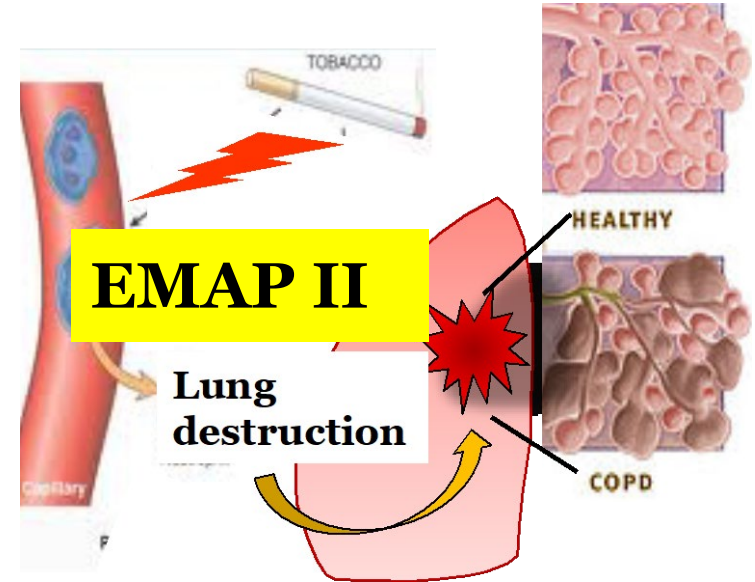
- * Rapid methods to determine infectious complications
- * Rapid methods to determine other life threatening complications (clot, MI)





Search for Biomarkers and Mediators of COPD/Emphysema

- **Chronic bronchitis** affects airways and breathing
- **Emphysema** reduces gas exchange and breathing
- Induced mainly by cigarette smoke exposure. Also caused by genetics (Alpha-1 Antitrypsin Deficiency) and HIV infection
- Progressive disease even after cessation of smoking
- Involves cell death and protease activation

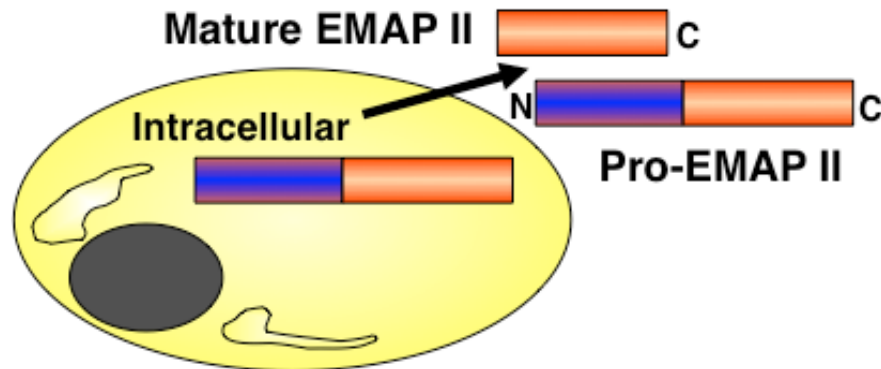


Diagnosis through:

- pulmonary function test (PFT)
- Computer tomography

Further Diagnostics:

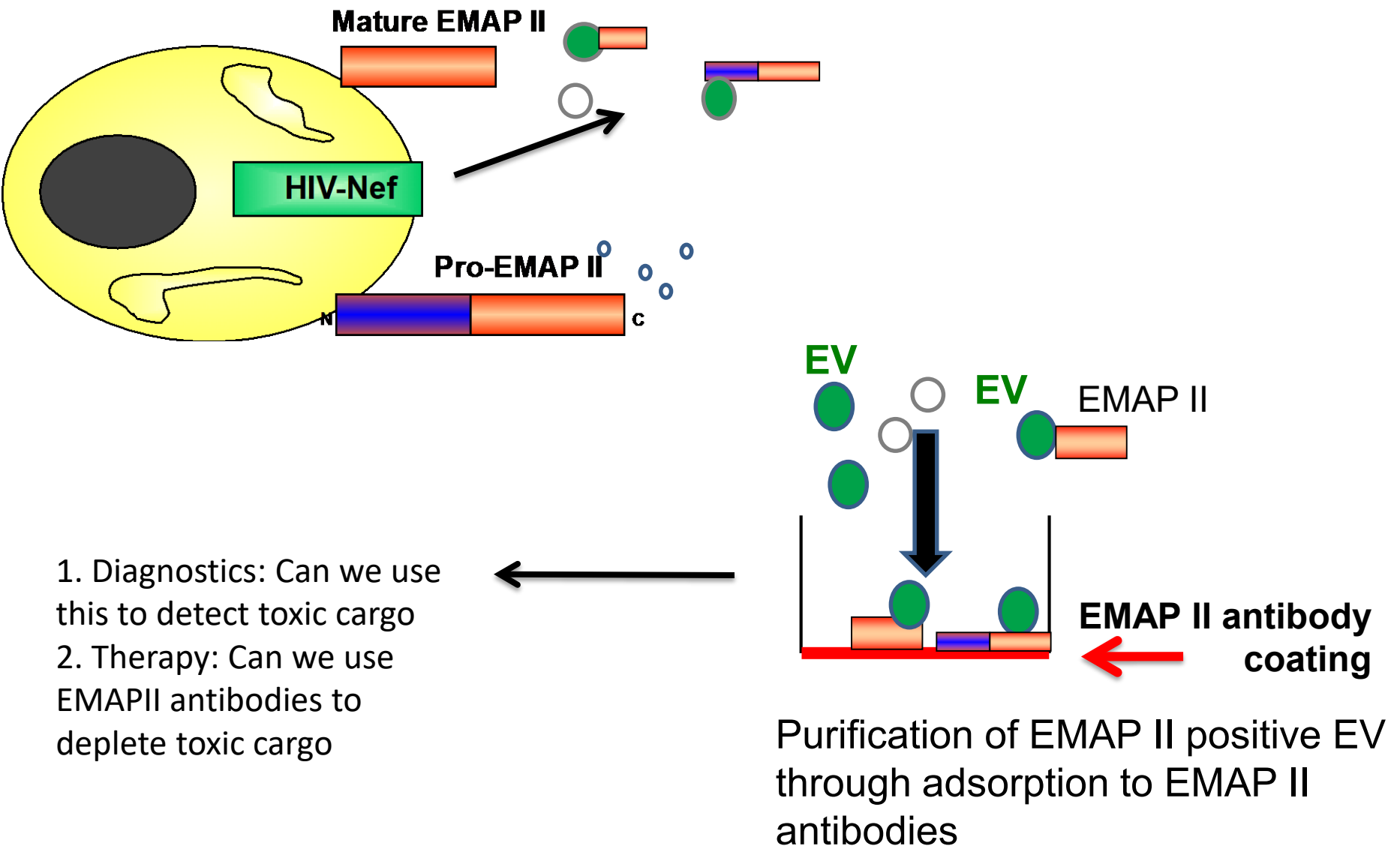
- Bronchoalveolar lavage fluid (BAL)
- Sputum samples



Problem 1: Plasma EMAP II does not match well with lung function

Problem 2: EMAP II exists on 1. surface of cells, 2. in solution, 3. exist as pro- and mature EMAP II

HIV-Nef expression Correlates with EMAPII in BAL Derived Cells and Extracellular Vesicles



Genomics, Bioinformatics and Data Sciences

Yunlong Liu, PhD

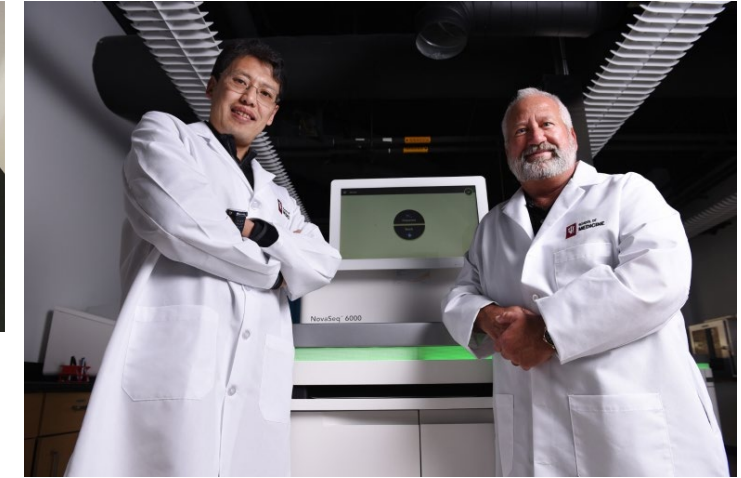
MMGE, CCBB, CMG, PHI

Kun Huang, PhD

HemaOnc, PHI, CCBB, CBMI

Center for Medical Genomics

sequencing • single cell • genotyping



Instruments		Services
Illumina	NovaSeq 6000 (2)	DNA-seq (WGS, WES, panels)
	HiSeq 4000	RNA-seq (mRNA, total RNA, FFPE, miRNA)
	NextSeq 500	ChIP-seq, CLIP-seq, ATAC-seq
	MiSeqDX	DNA methylation
Life Tech	Ion Proton	Metagenomics (16S, shotgun)
Oxford N	Nanopore MinION	long range/linked reads sequencing
10X	10X Chromium System	single cell/nuclei RNA-seq
Fluidigm	C1 (flow core)	single cell ATAC-seq
	CyTOF (flow core)	single cell CNV
		single cell protein markers
Qiagen	Qiasympany, ...	RNA/DNA extraction from blood
Beckman	Biomek FXP	library preparation for 96 samples in one batch
Hamilton	Microlab Star	

Mission

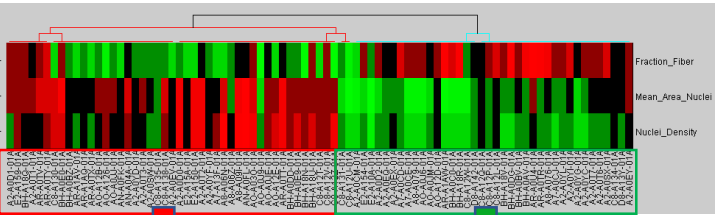
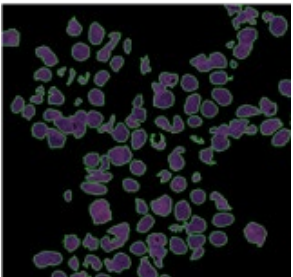
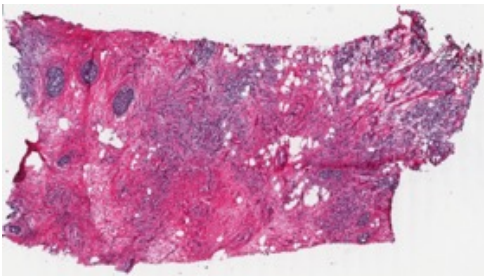
- High quality service
- Fast turnaround time
- Affordable price

2017-2018

- Project completed: **497**
- PIs served: **180**
- Total Revenue: **\$3.3 M**

PHI Data Science and Informatics

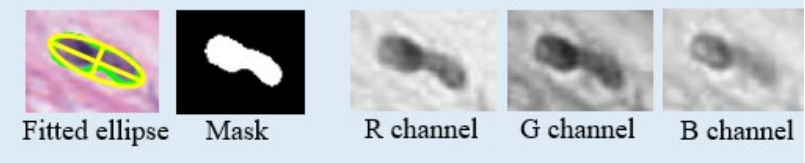
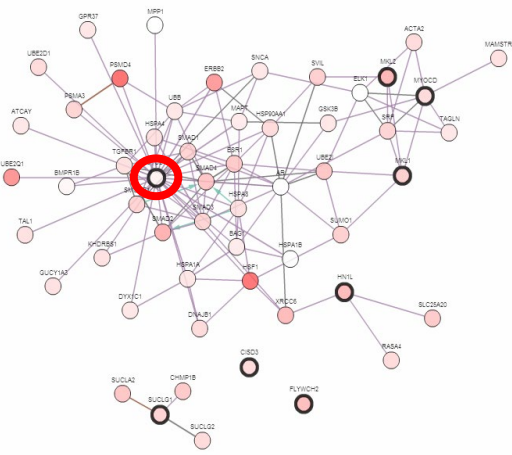
deep phenotyping • integration • AI • visualization



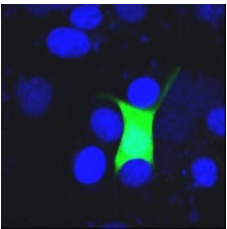
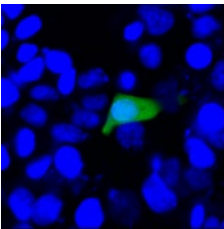
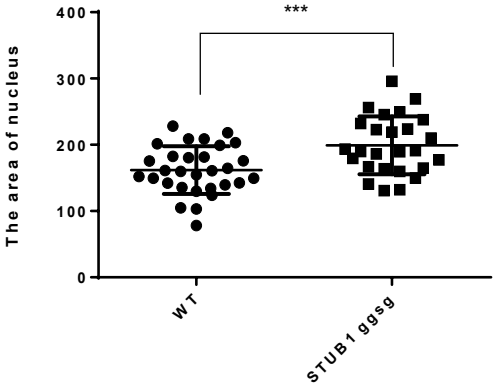
“High malignancy”
group

“Low malignancy”
group

Proteins	Cytoband
MYOCD	17p11.2
MKL1	22q13
MKL2	16p13.12
FLYWCH2	16p13.3
CISD3	17q12
HN1L	16p13.3
STUB1	16p13.3
SUCLG1	2p11.2



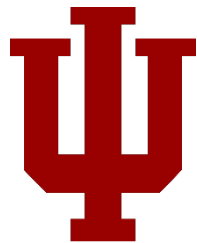
The size of nucleus 48h



Disease Diagnostics INventors Challenge

Chandan K Sen, PhD

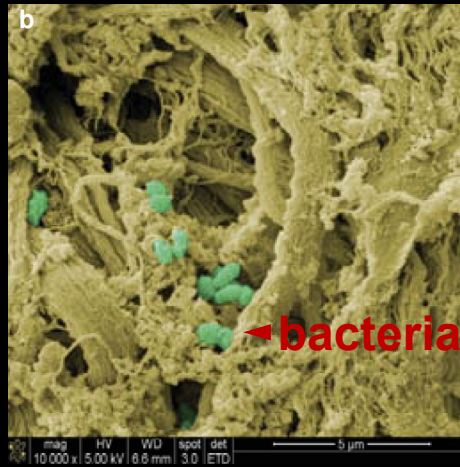
Executive Director, IU Health Comprehensive Wound Center



INDIANA UNIVERSITY

INDIANA CENTER FOR REGENERATIVE
MEDICINE AND ENGINEERING

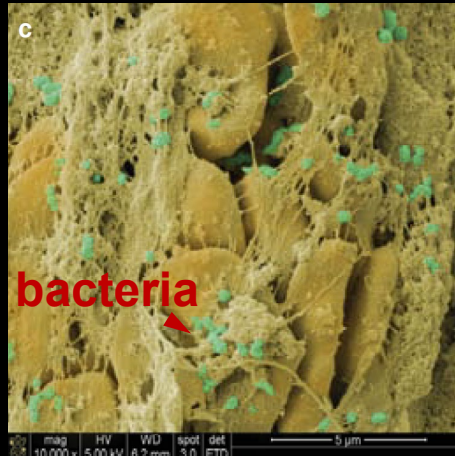
Wound Biofilm



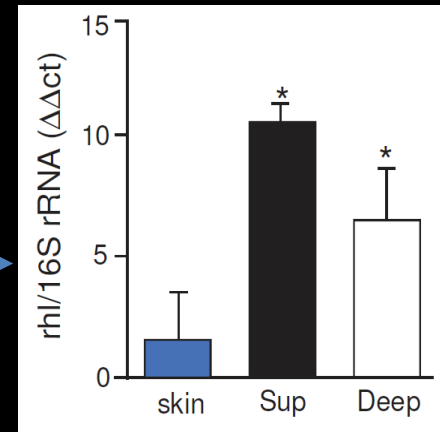
superficial layer



wound bed post-excision

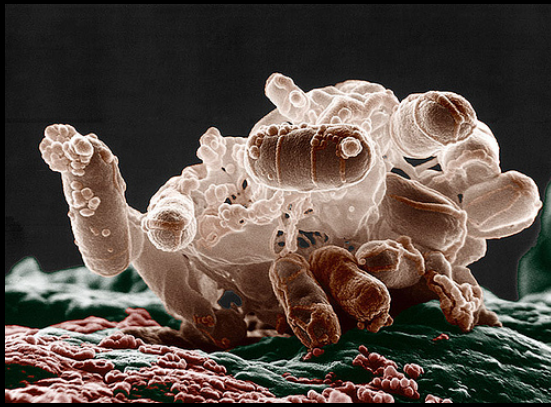


✓ *Pseudomonas aeruginosa* –Pyocyanin



Patient died
multiple organ failure



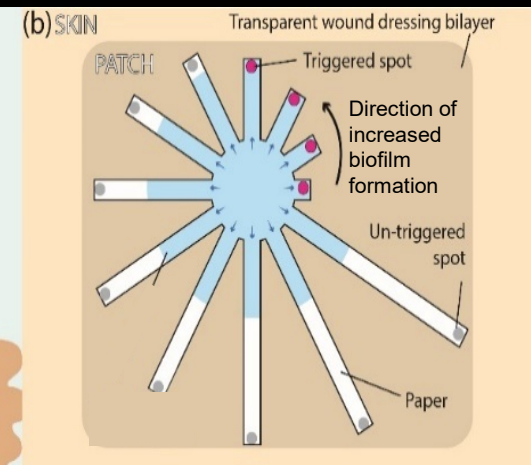
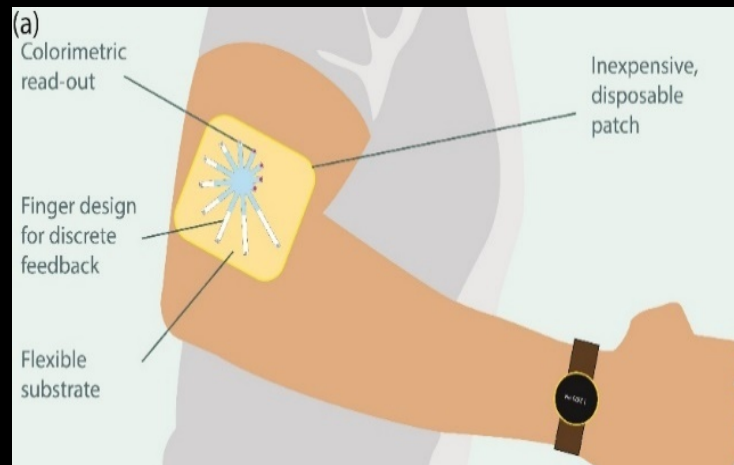
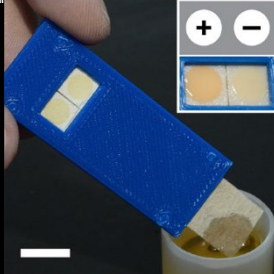
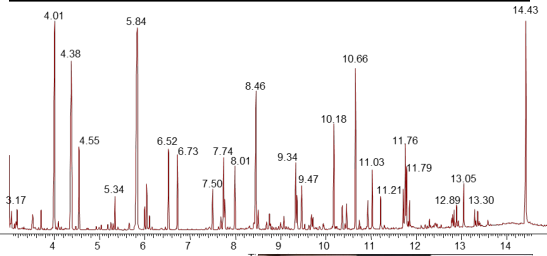
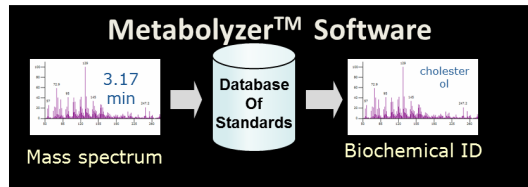
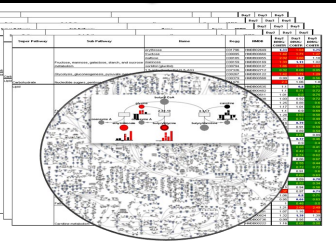


- ✓ *Pseudomonas aeruginosa* – *Pyocyanin*
- ✓ *Staphylococcus aureus* – *Leukocidin*
- ✓ *Acinetobacter baumannii* – *Porins (ompA)*
- ✓ *Klebsiella pneumonia* – *Enterotoxin*

can we detect bacterial signature?

wound metabolomics

Mass-customizable, low cost, disposable, colorimetric, chronological, in-situ biofilm detection system



Courtesy: Dr. Rahim, Purdue University



INDIANA UNIVERSITY SCHOOL OF MEDICINE

Supersoakers

Diagnosing and treating acute kidney injury through the development of controlled infusion technology to restore renal function.

Team Members: Robert Bacallao (IU), Mark Carlsen (Purdue), Mike Everly (Purdue)

Acute Kidney Failure

DIAGNOSTIC

↓ urine output + ↑ serum creatinine

CURRENT TREATMENT PLAN

watchful waiting

OUTCOMES

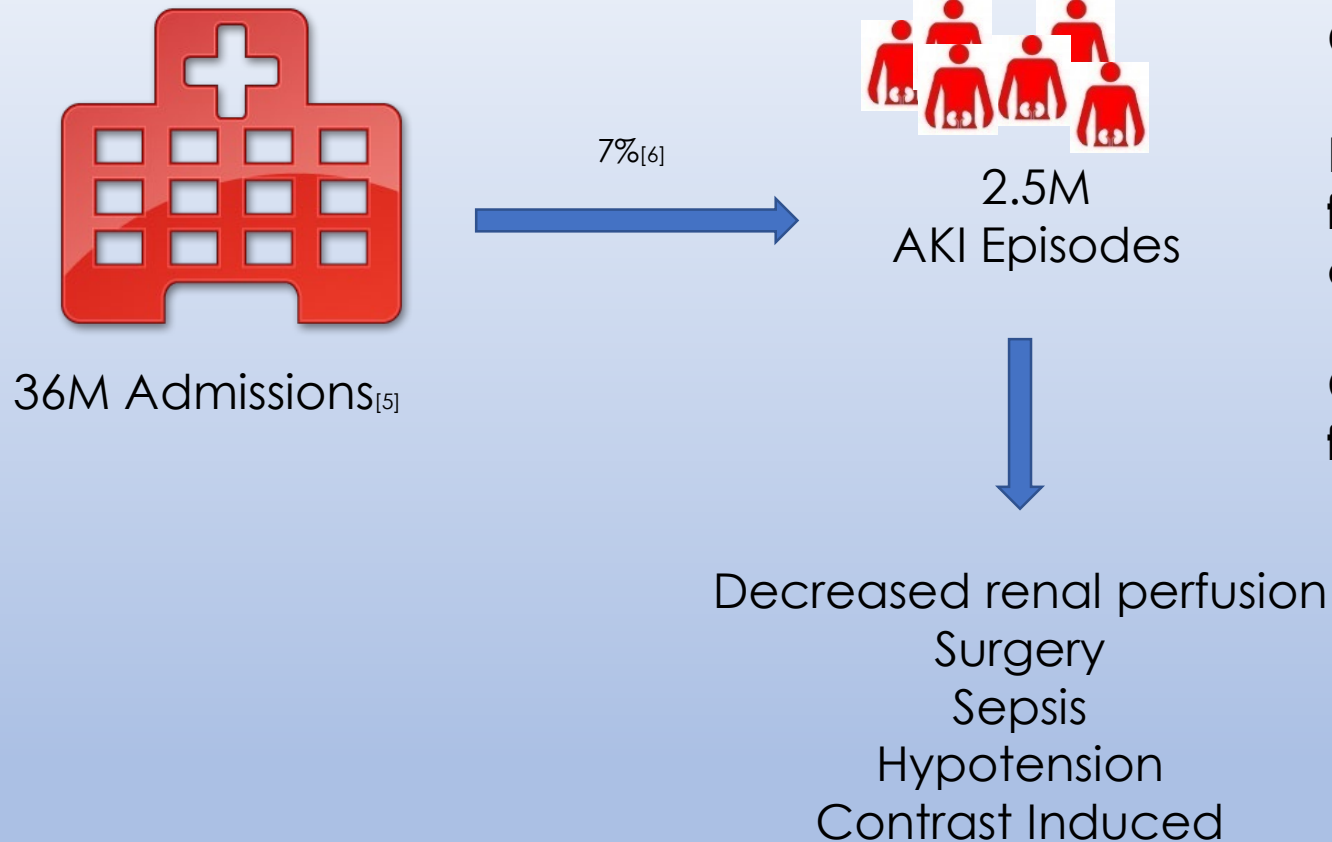
4x increase in length of hospital stay^[2]

4x increase in likelihood of transfer to ICU^[2]

2x of dialysis-requiring AKI incidence in past 10 years^[8]

7x increase in likelihood of death^[2]

Acute Kidney Failure

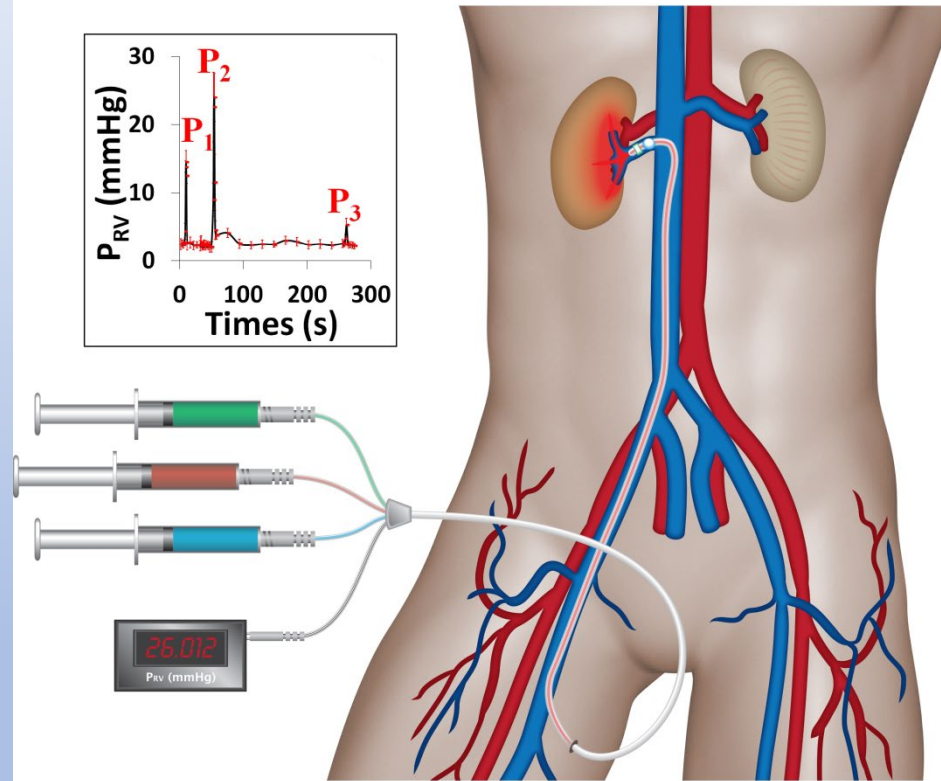


Current therapies:

Dialysis-doesn't reverse the acute kidney failure, it is expensive, it increases length of hospital stay.

Clearly there is a compelling market need for improvement in care.

Our Solution-a retrograde perfusion device that memorializes or experimental work



Current Status

- Programmable perfusion pumps have been purchased.
- Computer board is being assembled.
- Plan for ex vivo testing late January
- Plan for in vivo testing early March
- Design coordinated with lead catheter engineer

Ongoing challenges

- Need to raise monies for the next phase of development
 - Generation I catheter
 - Testing in porcine model of acute kidney injury
 - Team assembly for pre-clinical finishing of engineering design
 - FDA approval pathway needs to be identified.

THIS JUST IN!!!

- SBIR grant to perform studies in porcine model received a competitive score.
- Thanks to Dr. Sors, Shankar, Hess, and Moe for continued support.



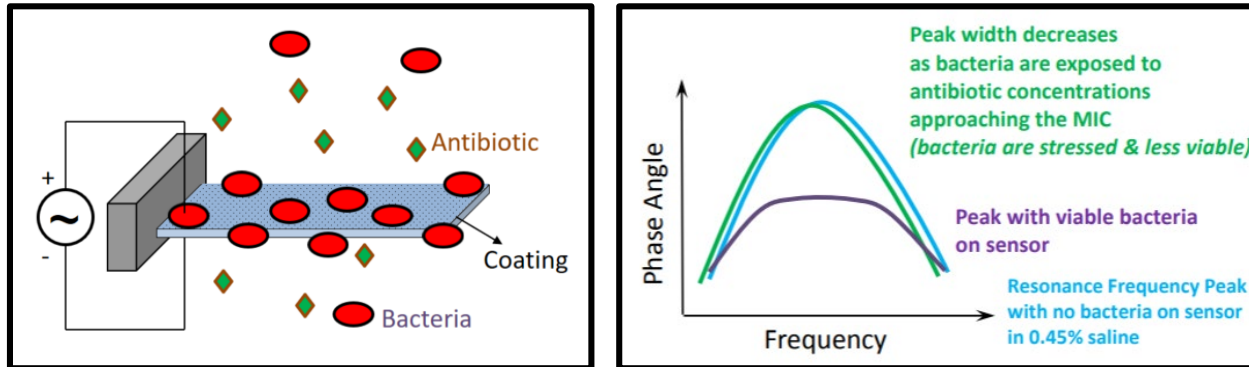
IU CPR Team Update

Aline Elquist¹; Jack G. Schneider, MD²; Christopher L. Emery, MD³; Na (Luna) Lu¹, Thomas E. Davis, MD³;

¹ Purdue University Sustainable Materials and Renewable Technology (SMART) Lab,
²Ryan White Center for Pediatric Infectious Disease and Global Health, Indiana University School of Medicine, ³Department of Pathology and Laboratory Medicine, Indiana University School of Medicine

iAST

Measuring electromechanical impedance for rapid antimicrobial susceptibility testing (AST)



- Expanded organisms and antibiotics tested
 - 6 organisms
 - 12 antibiotics: penicillins, cephalosporins, quinolones, carbapenems, monobactams, oxazolidinone, glycopeptide, glycyclcycline, lipopeptide
 - High correlation of results to standard methods – 92% within CLSI range*
- Developed a Matlab program to take multiple measurements at each antibiotic concentration for future testing. Total testing time is ~ 10 minutes



Milestones & Timeline

- **Milestone 1 – Complete**
 - Developed a testing procedure and software to analyze results rapidly
- **Milestone 2 – Complete protocols for PZT sensor – In progress**
 - Focus on sensor design and fabrication methods to improve consistency and reliability
 - Determine lower limit of detection (LOD)
- **Milestone 3 – Compare MICs and interpretive results – In progress**
 - Continue to expand organisms tested using iAST

Tasks	Mo. 1-3	Mo. 4-6	Mo. 7-9	M. 10- 12
Year 1 – Piezoelectric sensor for AST testing				
Milestone 1 – Proof of concept				
Milestone 2 – Complete protocols for PZT sensors				
Milestone 3 – Compare MICs and Interpretive results				



- Sensor fabrication – We are investigating new fabrication techniques that will allow for a more consistent and scalable approach to sensor fabrication
- Impedance analyzer communication – Computer programming for real-time, automated measurements and analysis has been a challenge.
- Software development – creating a user-friendly interface to automatically display the susceptibility and MIC
- Find a low-cost impedance analyzer for global implementation

A multiplex-able platform for bacteriuria by signal ion emission reactive release amplification (SIERRA)

Zane Baird¹, Zehui Cao¹, Gerald Denys², Christina Ferreira³, Michael Pugia¹

¹Indiana Biosciences Research Institute, 1345 W. 16th St. #300, Indianapolis, IN, USA

²IU Health and Pathology, 350 West 11th Street, Indianapolis, IN, USA

³Purdue University, Bindley Bioscience Center, 1275 3rd Street, West Lafayette, IN, USA

⁴Submitting lead organization: mpugia@indianabiosciences.org

The TEAM



Michael Pugia, PhD

IBRI

Research Fellow, Director of the
Single Cell Analytics Center (SCAC)

- 20 IVD product approvals
- 56 U.S. patents
- 34 active US applications
- 470 world wide patent filings



Zane Baird, PhD

IBRI

Staff Scientist - SCAC

- Device design and fabrication
- Instrumentation
- Assay development
- Mass spectrometry

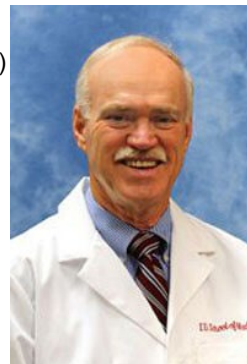


Zehui Cao, PhD

IBRI

Senior Staff Scientist - SCAC

- Molecular assay development
- Next Generation Sequencing (NGS)



Gerald Denys, PhD
IU

Professor of Pathology
and Laboratory
Medicine, IU Health and
Pathology

- Directed numerous clinical trial
- Clinical validation of novel microbiological assays



Christina Ferreira, PhD
Purdue

Lipidomics Research
Scientist, Purdue
University

- Metabolomic and lipidomic profiling
- High-throughput MS screening

Need for rapid & accurate bacteriuria analysis

Disease Burden

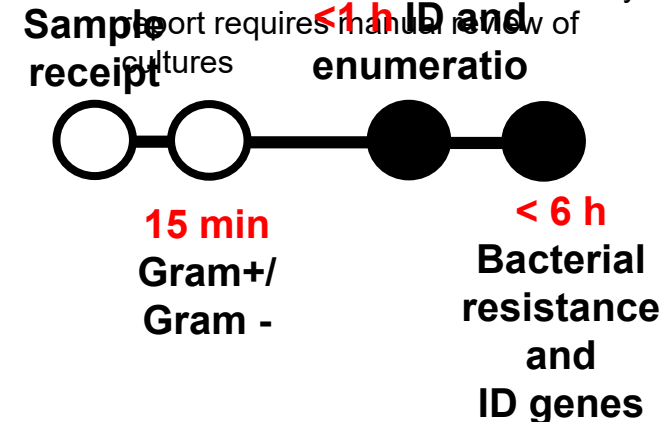
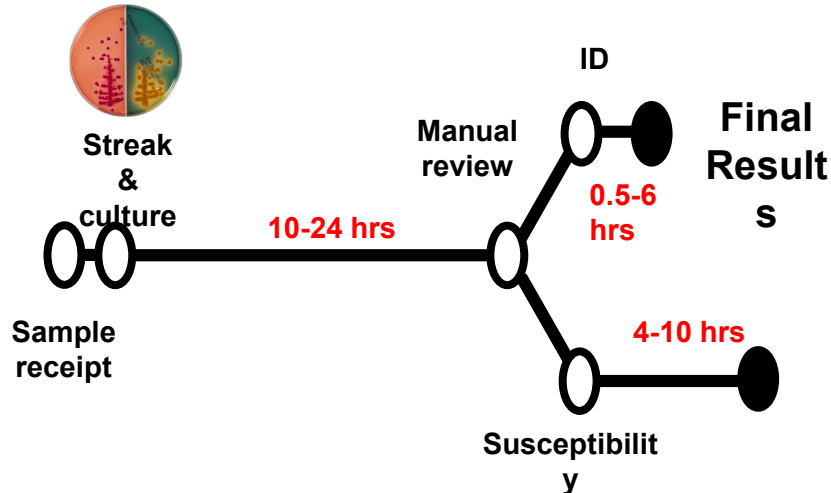
- \$3.5B annual (2015)
- \$464M Pediatric (2011)
 - 18.6% annual increase from 2006-2011
- Leading cause of renal disease

Treatment and risks

- Antibiotic resistance due to 30-60% of prescriptions being unnecessary
- B-Lactams only effective for gram(-)
- Broad spectrum cause microbiome disruption

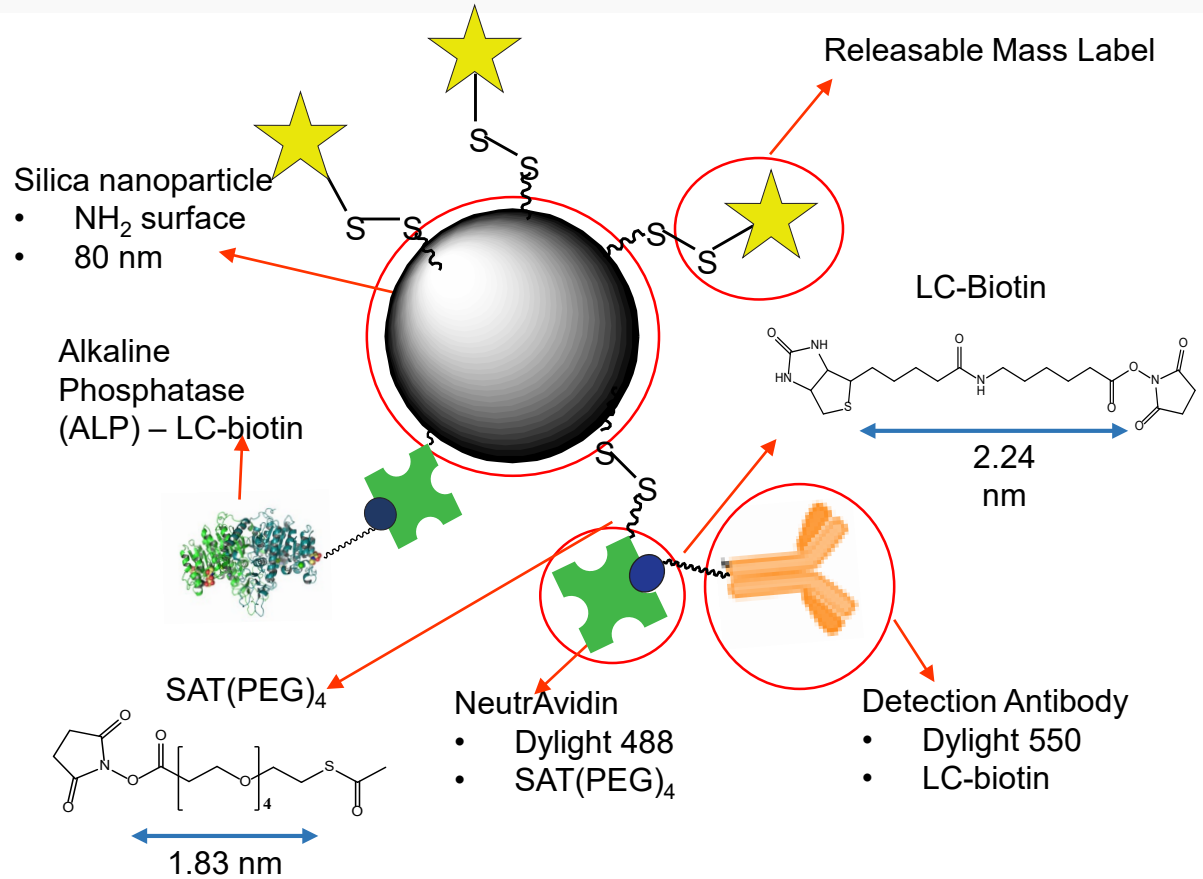
Diagnostic problems

- Treat based on symptoms
- Only culture positive urinalysis which has a 46 % PPV & does not detect Gram (+)
- Lab runs ~600 samples/day and only ~30% positives confirmed
- Negative strip leads to expensive molecular testing (\$1200/patient) but still no culture
- 24-48 hrs to culture result & 3 -5 day to report requires manual review of cultures



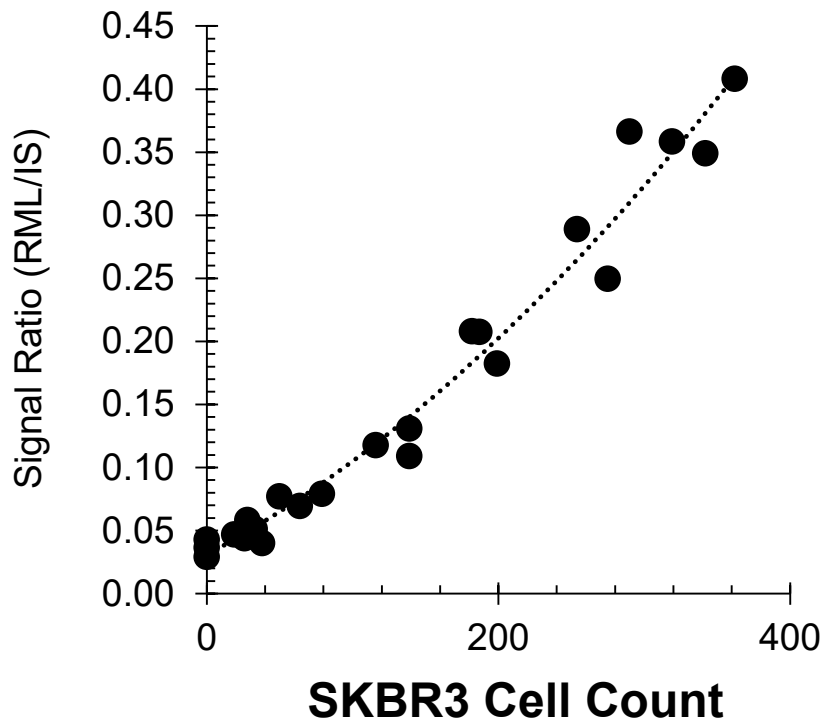
Signal Ion Emission Reactive Release Amplification Nanoparticles

- Mass Spectrometric Immunoassay (MS-IA) based on releasable mass labels (RML)
- Multiplexable quantitation at LAB for uorpathogens without culture
- Electrochemical Immunoassay (EC-IA) for POC for gram -/+ with out culture
- Non-destructive and PCR, & NGS compatible for DNA/RNA analysis
- 10^3 amplification over high sensitivity chemiluminescence

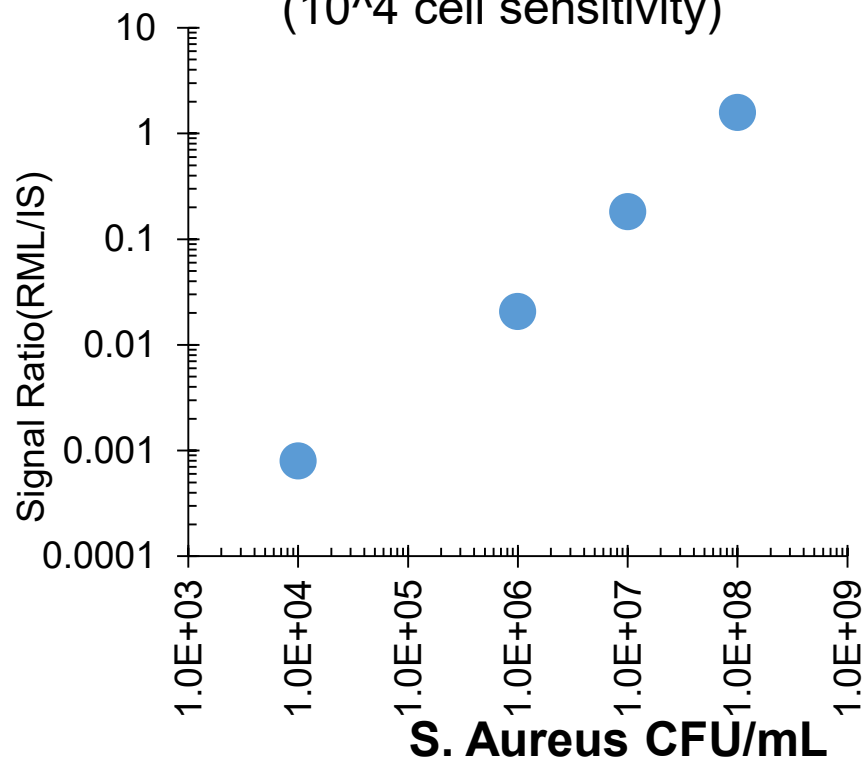


Cell detection using SIERRA Nanoparticles

MS-IA response for cancer cells
(25 cell sensitivity)

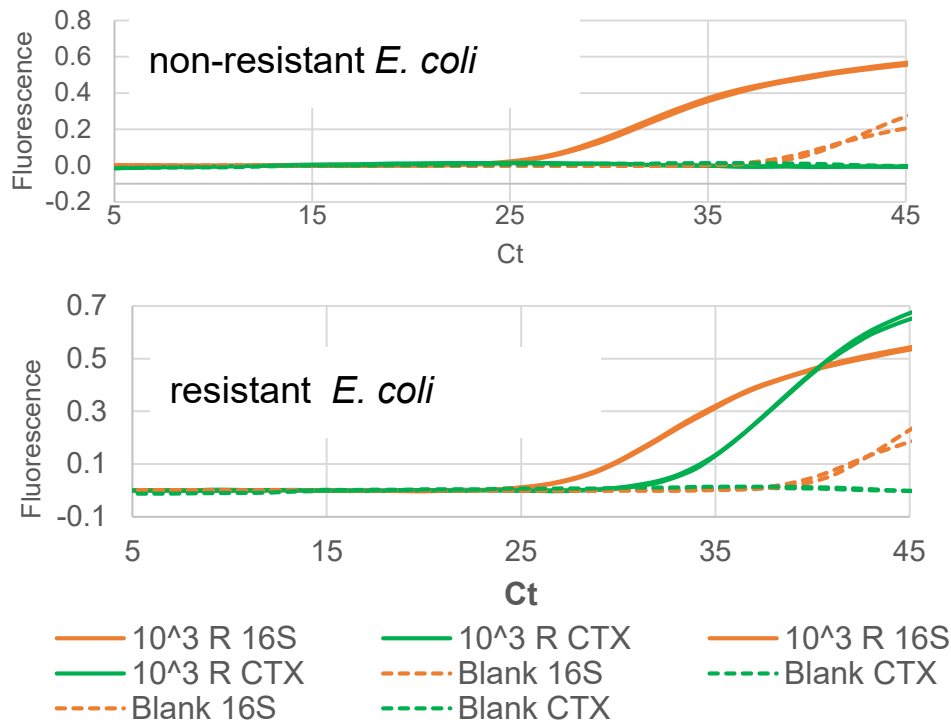


MS-IA response for *S. Aureus*
(10^4 cell sensitivity)

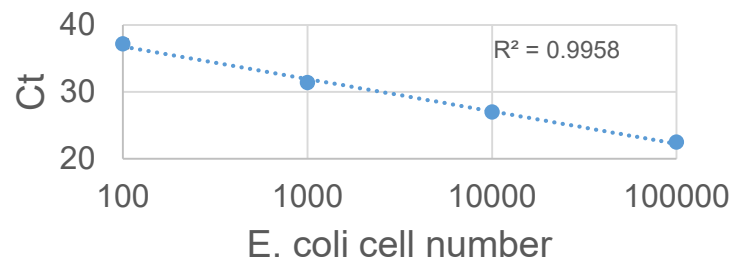


Bacterial DNA analysis after MS-IA or EC-IA

qPCR for CTX-M AMR gene and 16S amplification for 10^3 *E. coli*



Quantification of CTX-M AMR gene from resistant for $> 10^2$ *E. coli*



16S sequencing shows strain differences

Partial 16S sequences of the non-resistant and resistant strains. Mostly identical but highlighted shows sequence differences:

```
>Non-resistant_16S
GGTAGTCCACGCCGTAAACGATGTCGACTTGAGGTTGTGCCCTTGAGGCGTGGCTTCCGGAGCTAACCGGTTAA
GTCGACCGCCTGGGGAGTACGGCCGCAAGGTTAAACTCAAATGAATTGACGGGGGCCGCACAAGCGGTGGAG
CATGTGGTTTAATTTCGATGCAACGCGAAGAACCTTACCTGGCTTTGACATCCACGAAGCTTTTCAGAGATGAGAAATG
TGCCTTCGGAACGTGAGACAGGTGCTGCATGGCTGCTGCAGCTCGTGTGTGAAATGTTGGGTTAAGTCCCG
AACGGCGCAACCAAC
>Resistant_16S
GGTAGTCCACGCCGTAAACGATGTCGACTTGAGGTTGTGCCCTTGAGGCGTGGCTTCCGGAGCTAACCGGTTAA
GTCGACCGCCTGGGGAGTACGGCCGCAAGGTTAAACTCAAATGAATTGACGGGGGCCGCACAAGCGGTGGAG
CATGTGGTTTAATTTCGATGCAACGCGAAGAACCTTACCTGGCTTTGACATCCACGAAGCTTTTCAGAGATGAGAAATG
TGCCTTCGGAACGTGAGACAGGTGCTGCATGGCTGCTGCAGCTCGTGTGTGAAATGTTGGGTTAAGTCCCG
CAACGGCGCAACCAAC
```

Best Practices for Dx Challenge

Connect technology to clinical application by starting with diagnostic problem

Review standards of practice and latest approaches in clinic

Develop key performance features needed for ideal solution

Talk to key product developers to avoid pit-falls in your approaches

Outline grant application and papers goals at start to get proof of principle done

Assess real world testing environment with KOL and identify opportunities to challenge the technology

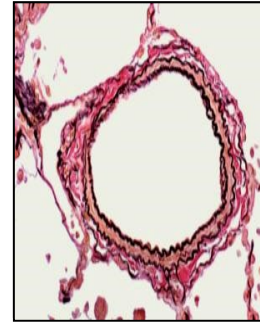
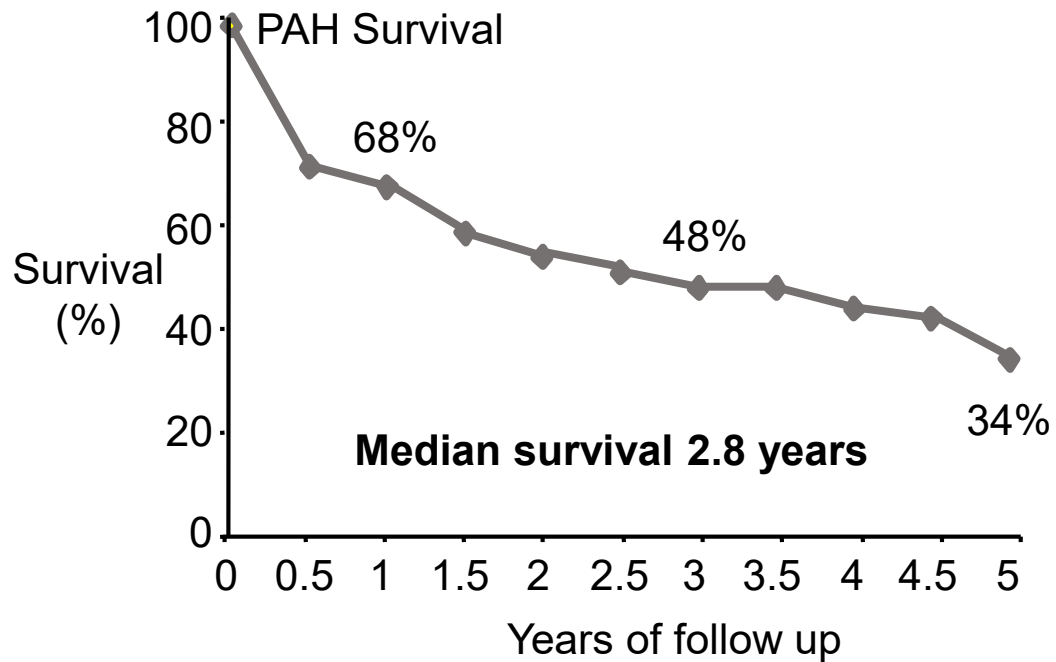


Developing new Therapies for Pulmonary Arterial Hypertension

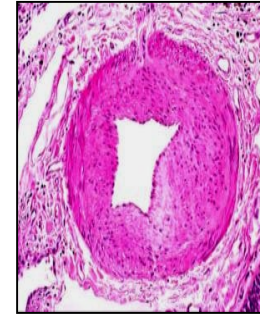
Roberto Machado (robmacha@iu.edu)

Tom Driver (tgd@uic.edu)

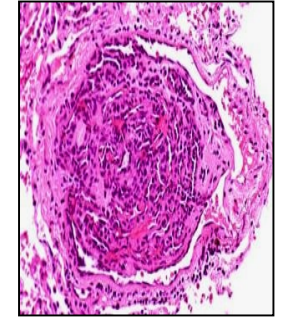
PAH Kills and Current Therapies Mostly Treat Symptoms



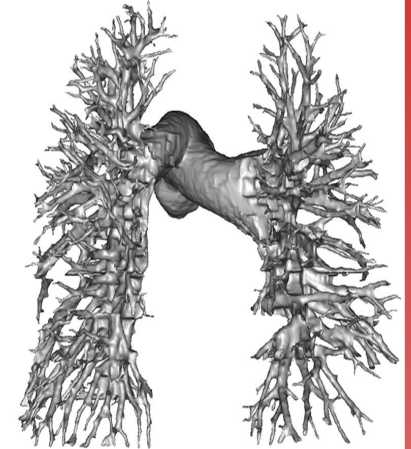
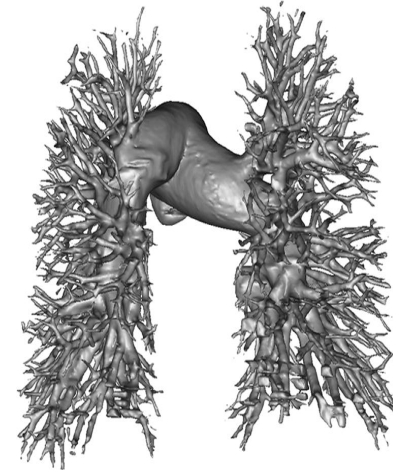
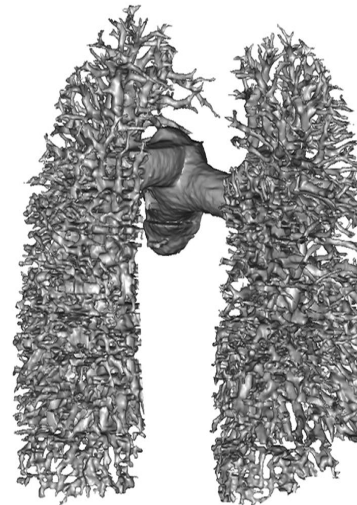
Normal



Moderate



Severe

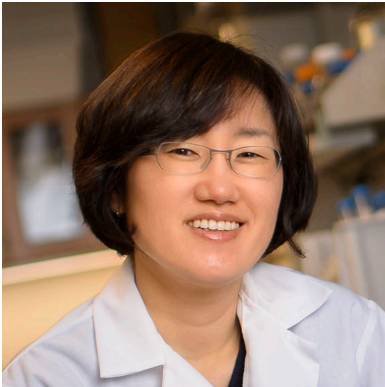


Reversing pulmonary vascular remodeling is an unmet need

NAMPT Promotes Pulmonary Vascular Remodeling and NAMPT Inhibition Reverses Pulmonary Vascular Remodeling in Severe Experimental PH models

Can we develop a lung/vascular targeted delivery system?

Nanoparticle Drug Delivery



Yoon Yeo, PhD

Associate Professor
Industrial and Physical Pharmacy
Purdue University

