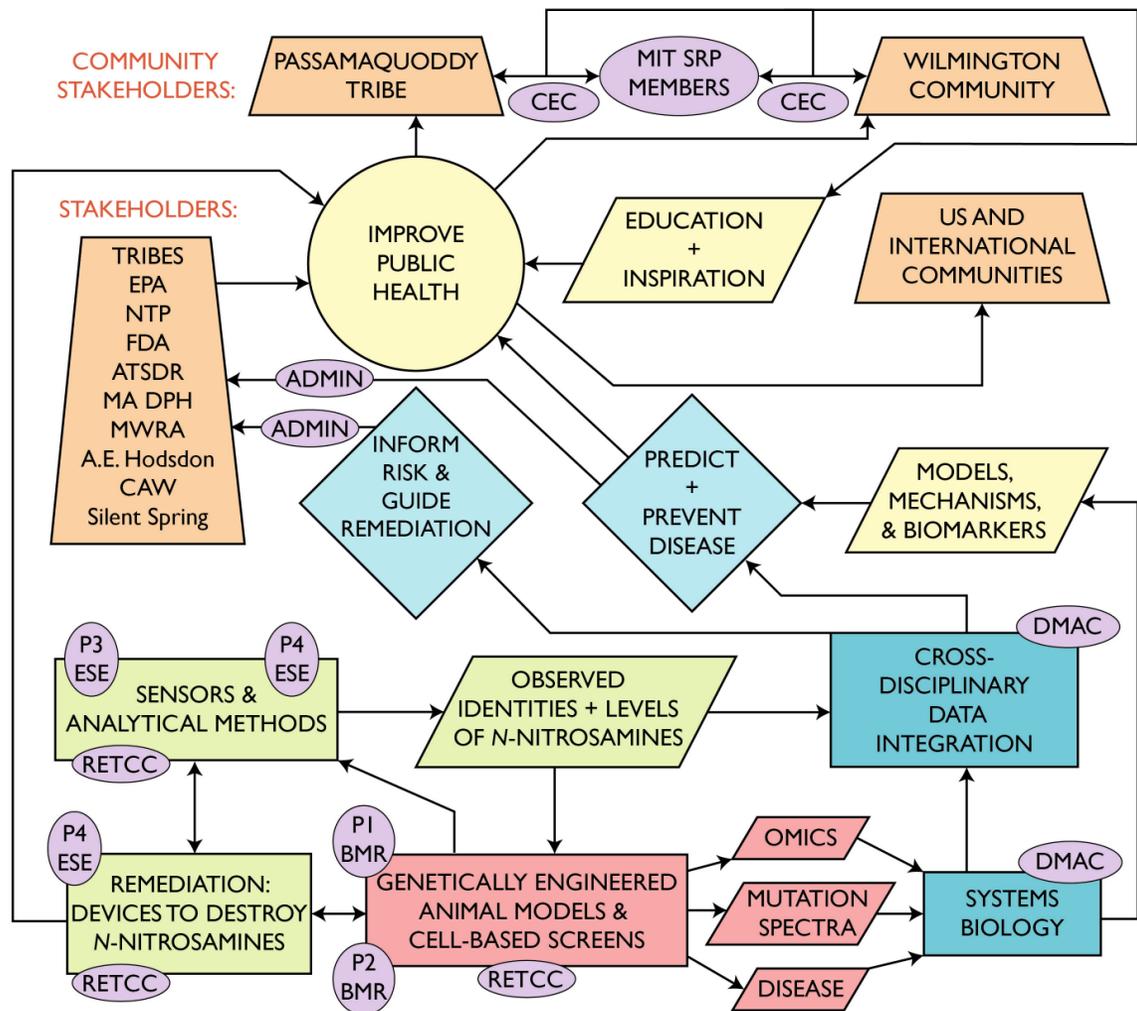


MIT Superfund Center Organizational Structure



The MIT Superfund Research Program: A Systems Approach for the Protection of Human Health from Hazardous Chemicals

Bevin P. Engelward, Sc.D.
 Director, MIT Superfund Research Program
 MIT Department of Biological Engineering

Desiree D. Plata, Ph.D.
 Deputy Director, MIT Superfund Research Program
 MIT Dept. of Civil and Environmental Engineering

John Essigmann, Ph.D.
 Deputy Director, MIT Superfund Research Program
 MIT Depts. of Biological Engineering and Chemistry



National Institute of
 Environmental Health Sciences
Superfund Research Program

Many thanks to Michelle Heacock and Leroy Worth!

Disclosure

Bevin Engelward is a co-Inventor on the CometChip Patent

Motivation for Focus on *N*-Nitrosamines
Communities we Learn from and Support
How NDMA Damages the Genome
Mission
Projects
Cores
Team
Our Systems Approach

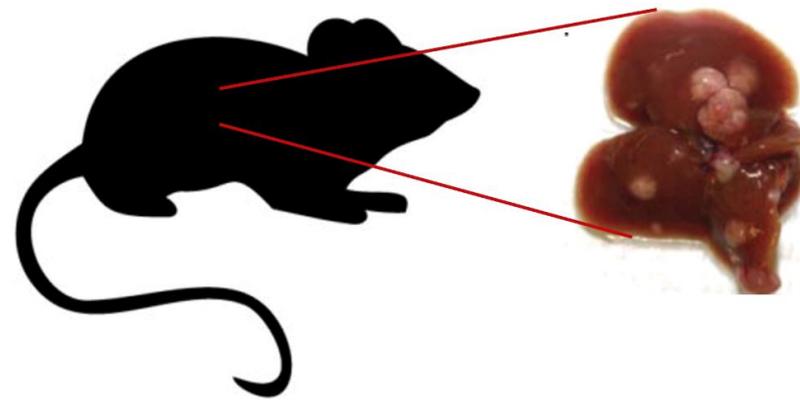
Motivation for Focus on *N*-Nitrosamines
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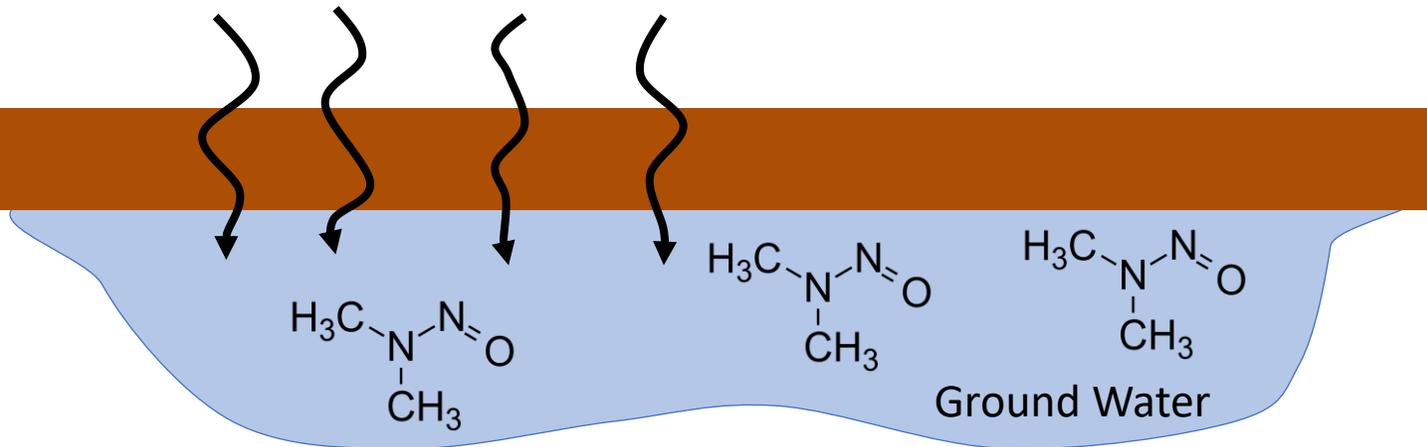
Members of the community, identified NDMA as a possible cause of childhood cancer



NDMA is a Potent Carcinogen in Animal Models



National Polychemicals, Inc. 1967



NDMA

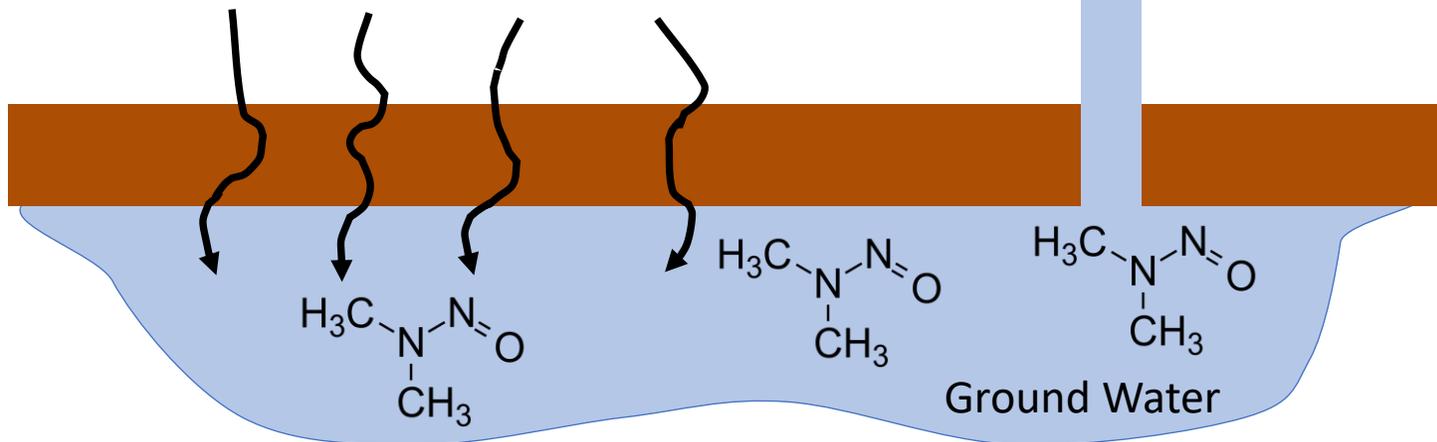
N-nitrosodimethylamine

N-nitrosodimethylamine (NDMA) was a Concern



National Polychemicals, Inc. 1967

Alarming rates of childhood cancer



Olin Chemical became a Superfund Site in 2006

Wells were closed in 2002



News Releases from Region 1

Wilmington Mass. Olin Chemical Site Added to National Superfund List

Release Date: 04/18/2006

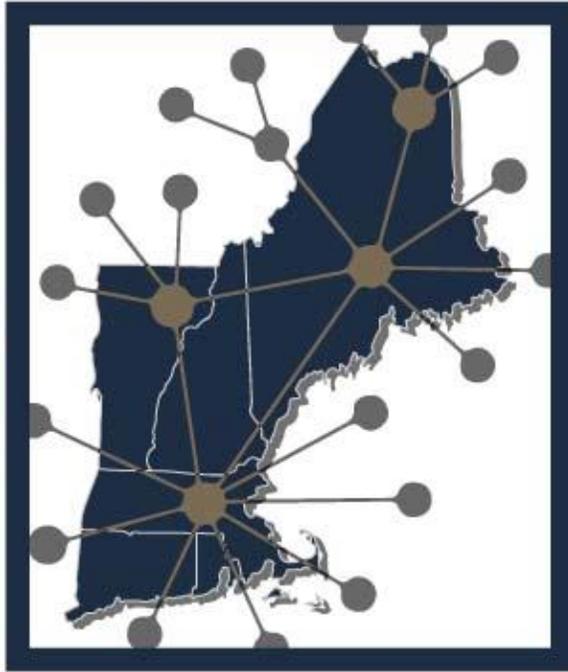
Contact Information: David Deegan, (617) 918-1017

(Boston, Mass. - Apr. 18, 2006) – Wilmington’s **Olin Chemical** Site is one of six sites nationwide being formally added to the Superfund National Priorities List (NPL) by EPA.

The NPL is EPA’s list of the country’s most serious hazardous waste sites, identified by the federal government for possible long term cleanup. Today’s completion of the NPL listing process ensures that a rigorous investigation of all environmental issues surrounding the site will be performed.

"The **Olin Chemical** listing is a positive milestone in the cleanup of the site and is good news for the south Wilmington and north Woburn communities," said Robert W. Varney, regional administrator for EPA's New England office. "EPA is deeply concerned with the damage caused to the Town of Wilmington’s primary drinking water aquifer. Designation of the **Olin Chemical** property as a Superfund site provides us with the technical, financial and legal tools needed to work closely with state and local stakeholders to ensure a complete and thorough investigation of the site, and a successful implementation of any cleanup plan that follows."

SRP



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Wilmington Environmental Restoration Committee (WERC)



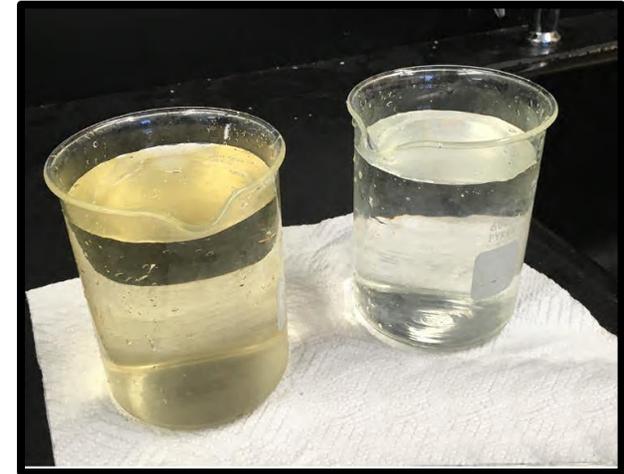
Photo by CEC Leader, Dr. Kathy Vandiver



Former Chief,
Maggie Dana



Passamaquoddy use wells
to get drinking water.



The method used to treat their
water is to use high levels of
chloramination, which leads to
formation of NDMA.

Work is underway to improve
water quality.

Motivation for Focus on *N*-Nitrosamines
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How NDMA Damages the Genome

Mission

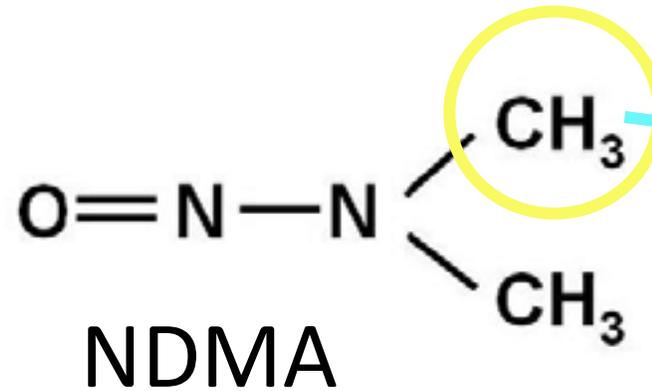
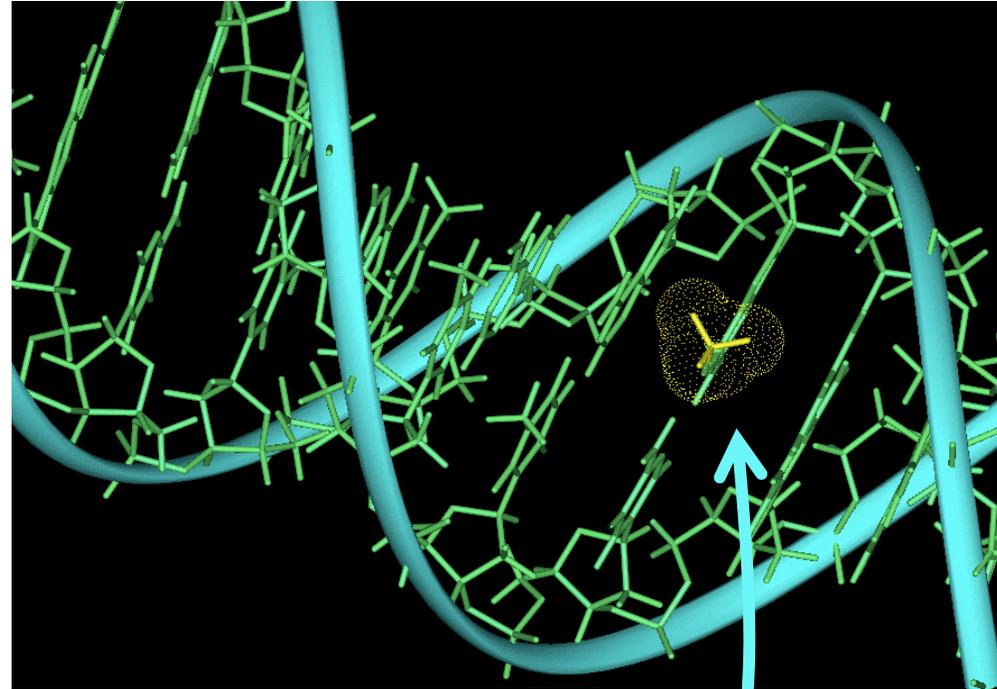
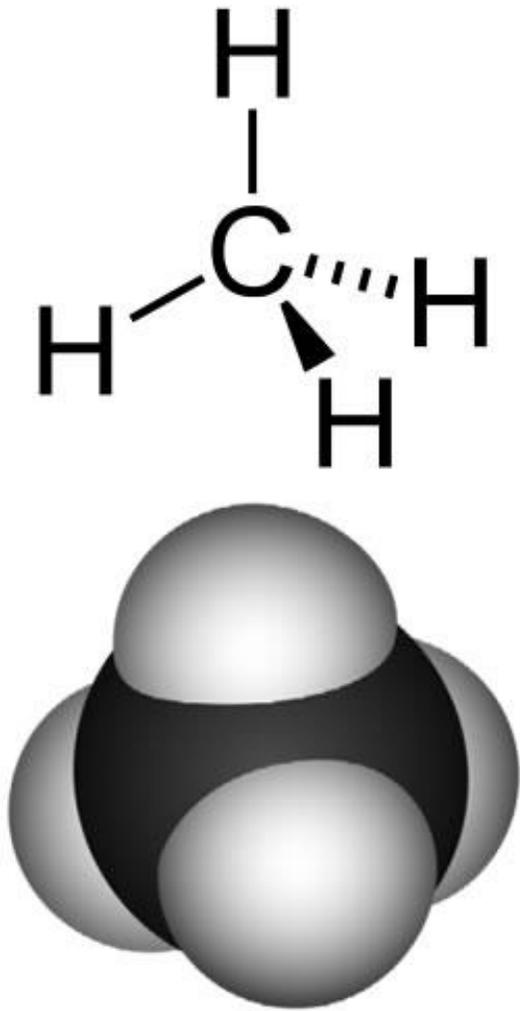
Projects

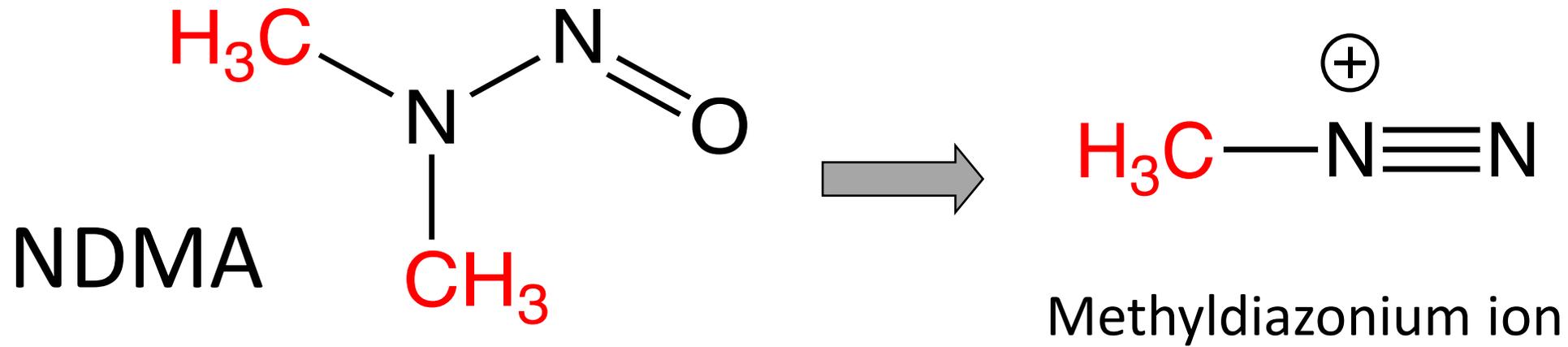
Cores

Team

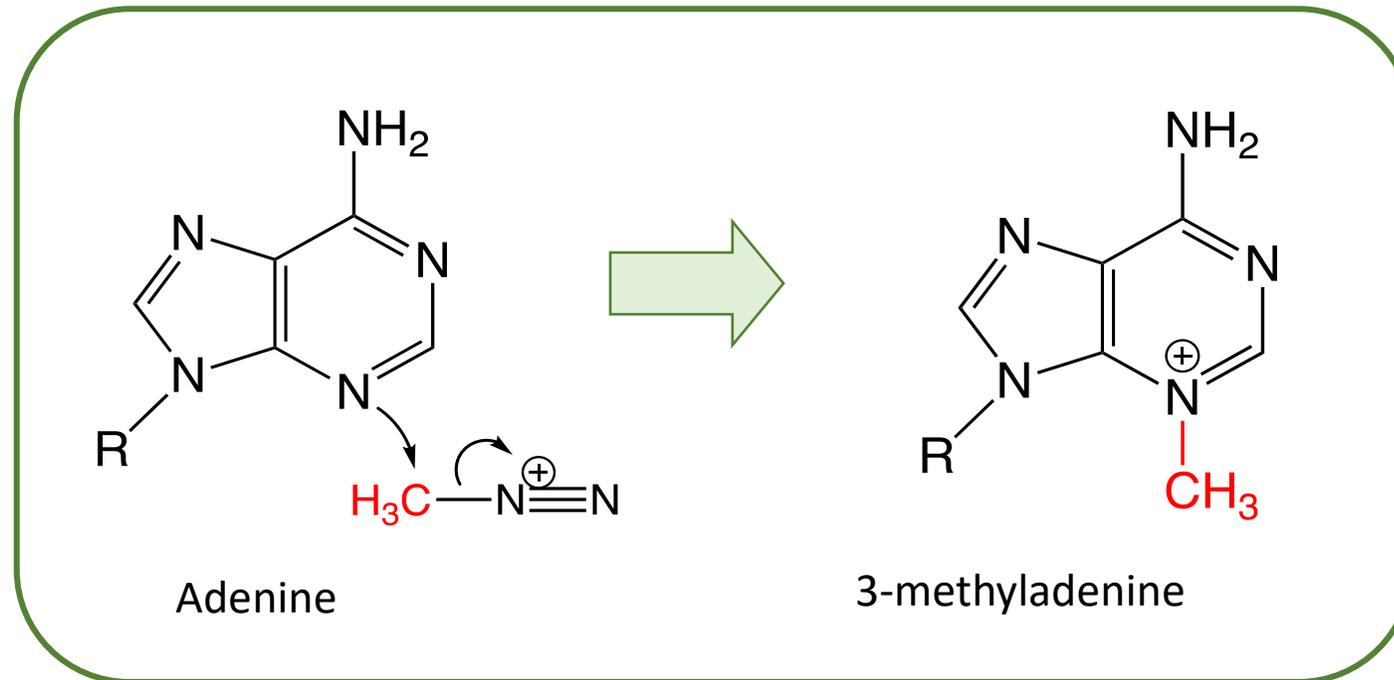
Our Systems Approach

N-nitrosodimethylamine (NDMA) creates 3MeA

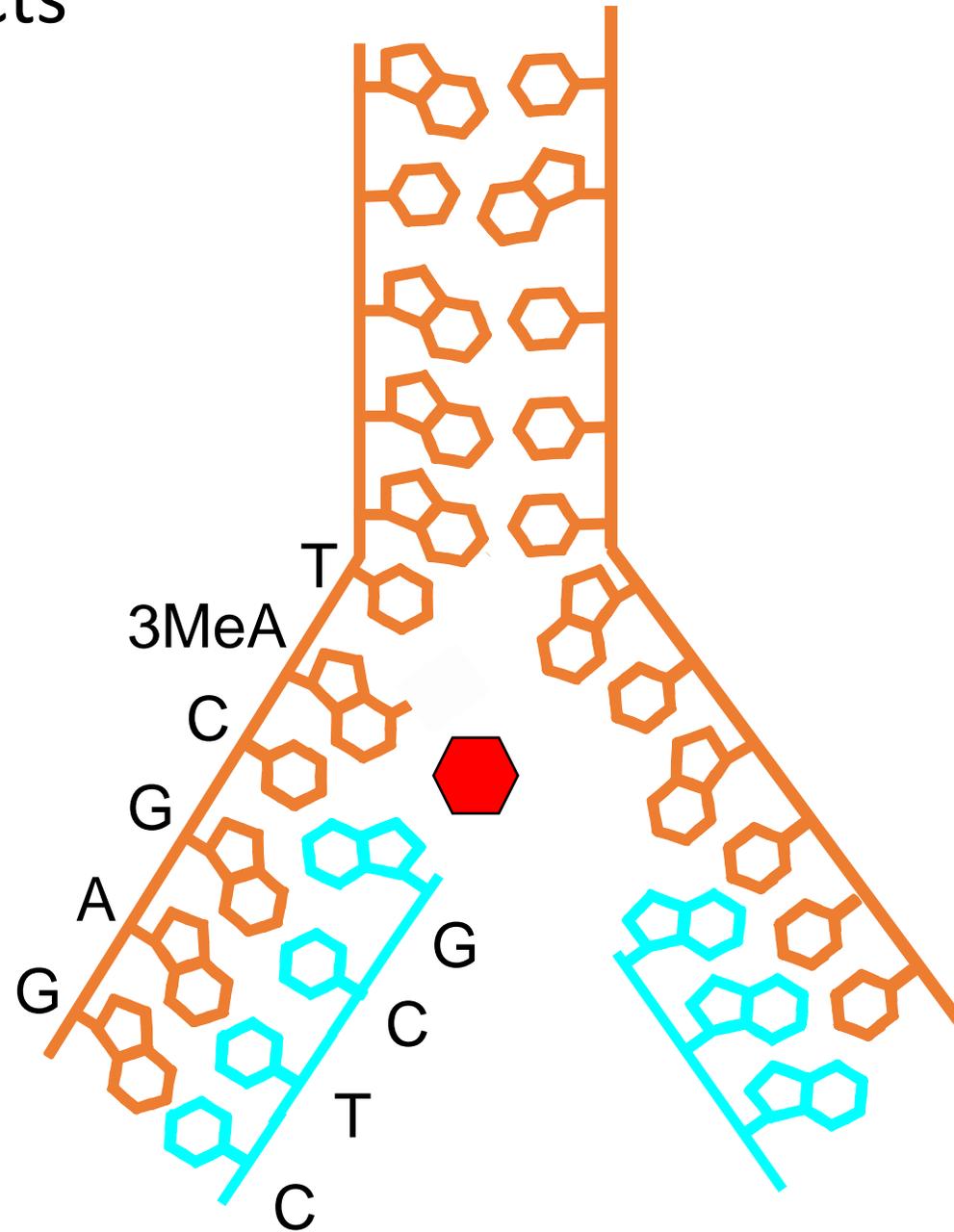
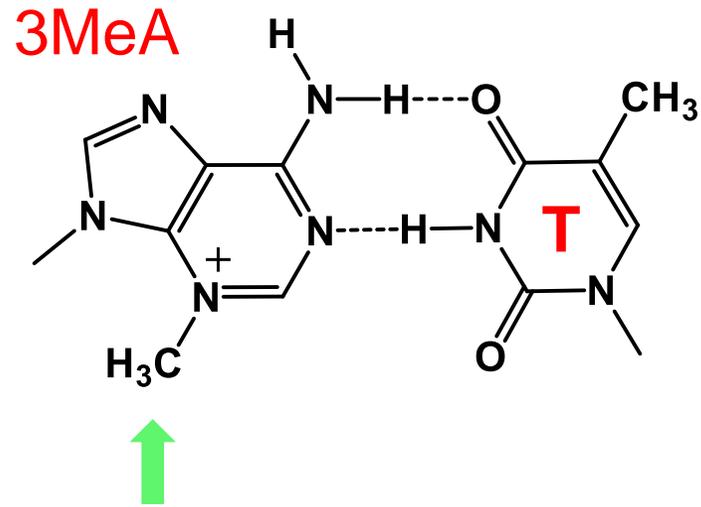




One out of several types of DNA damage.



Methyl Groups: Tiny Adducts with Big Consequences



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Team

Our Systems Approach

Our Mission

The Challenge:

Millions of people are exposed to environmental contaminants as a result of past industrial activities.

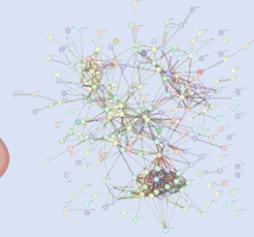
Our Vision:

We will create technology to sense and destroy contaminants
& to predict and prevent disease.

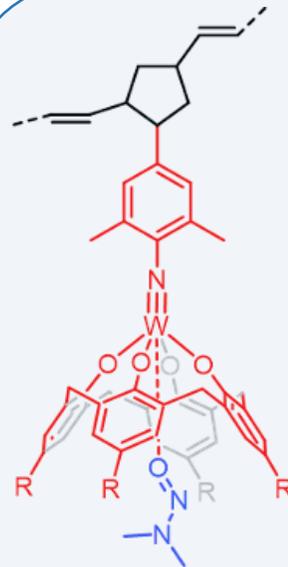
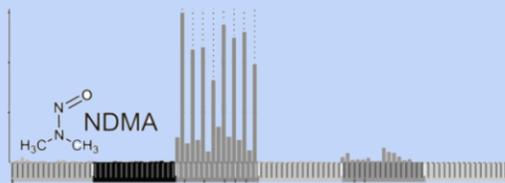
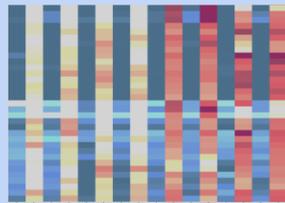
Our Impact:

Knowledge of Susceptibility Factors
Predictive Biomarkers
Animate Sensors
Environmental Sensors
Cleaner Water

Project 1: Engineered Mice and Cells
to Reveal Biological Responses
& Prevent Disease

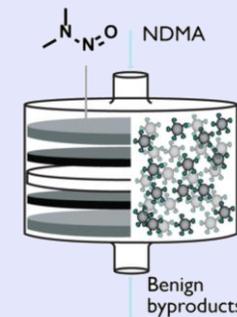
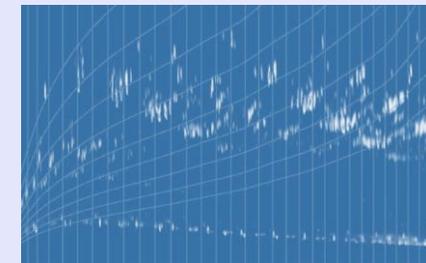


Project 2: Mutation Spectra
& Multi-Omics for Etiology & Prediction



Project 3:
Concentrators and Sensors
for Research & Citizen Science

Project 4: Measurements &
Engineering to Detect
and Prevent Exposure



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Project 1

Trainees:



Aimee Moise



Dr. Lee Pribyl



Joshua Corrigan
Key Collaborator



Dr. Lindsay Volk



Dr. Vandana Singh

P1 Leaders:



Prof. Bevin Engelward



Prof. Leona Samson

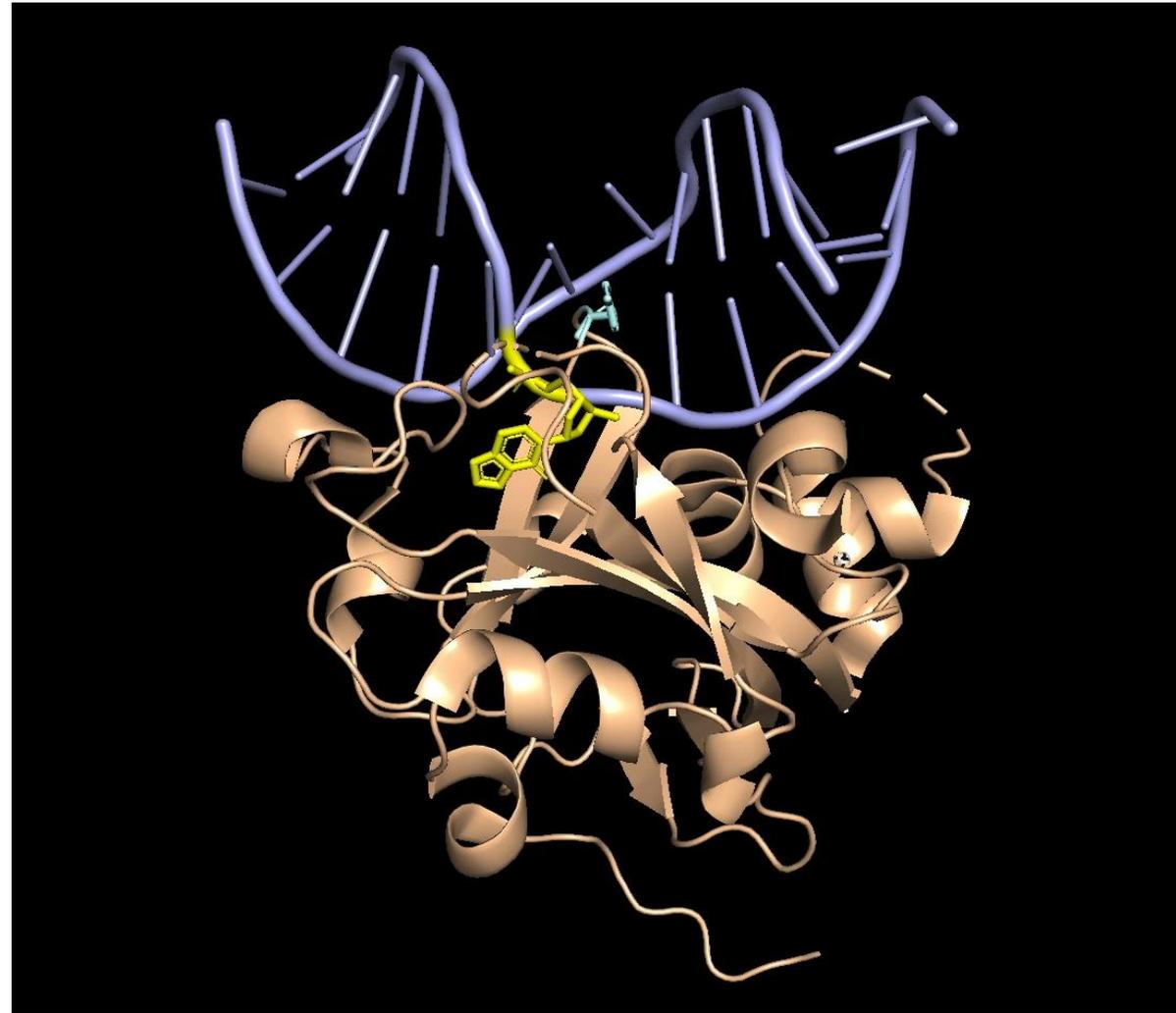


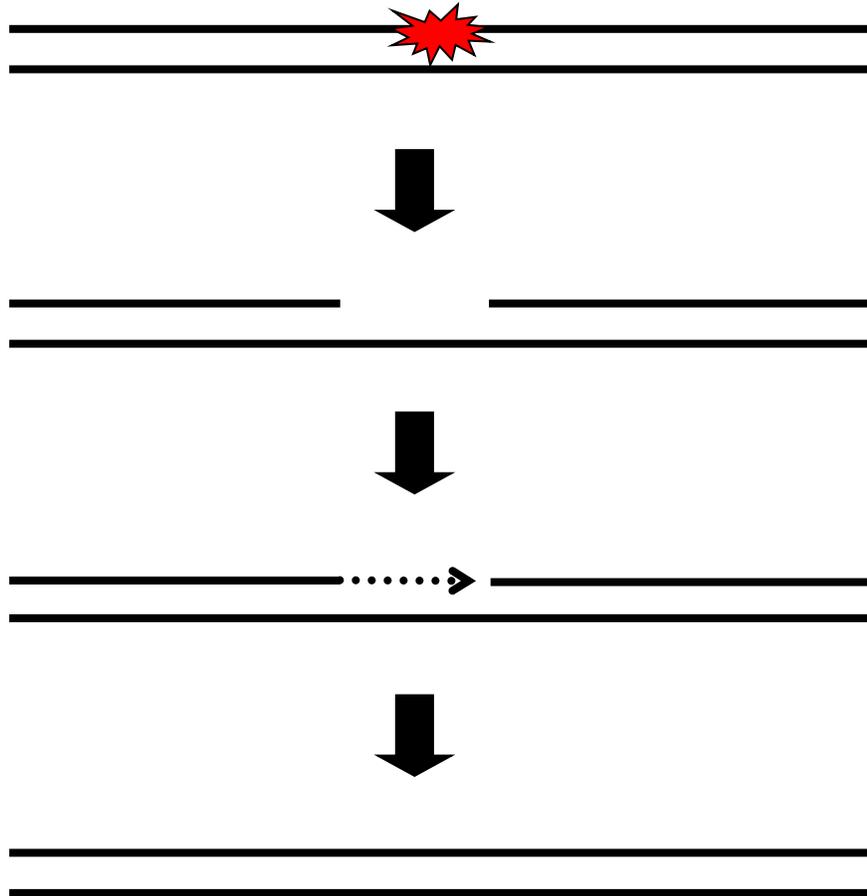
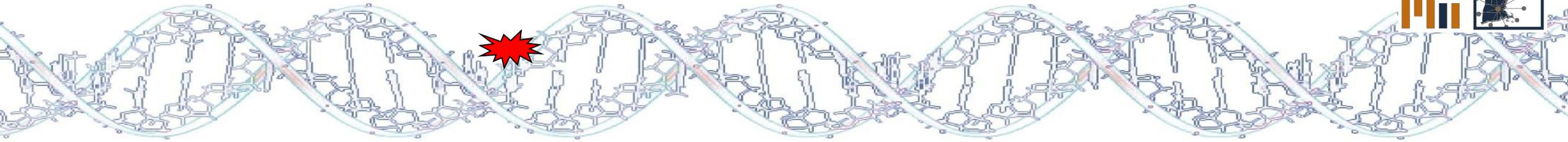
Prof. Bryan Bryson



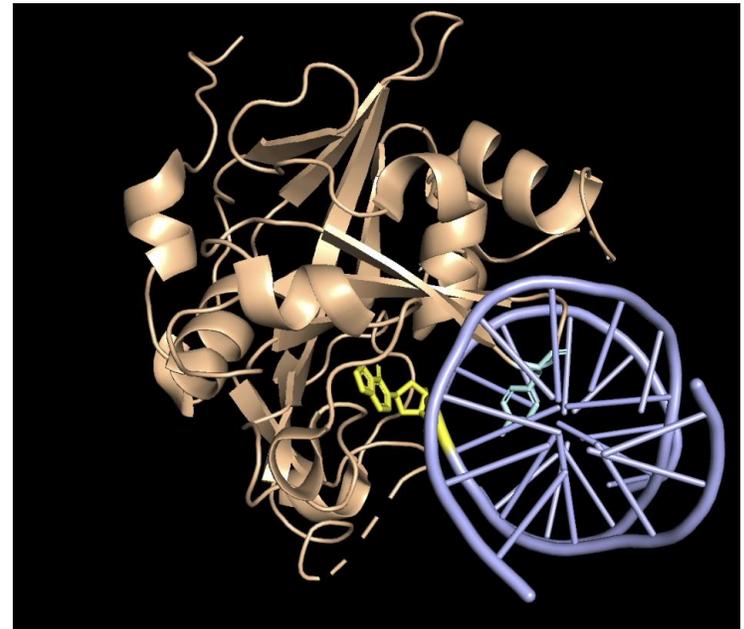
Dr. Susan Erdman

NDMA-Induced DNA Damage is Repaired by AAG, a DNA Glycosylase



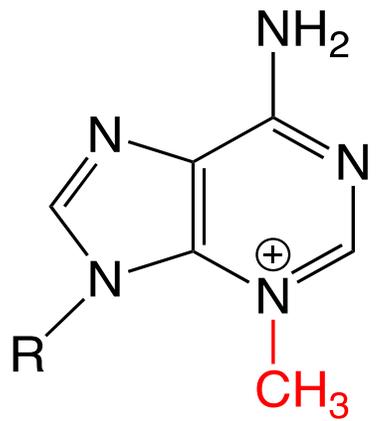
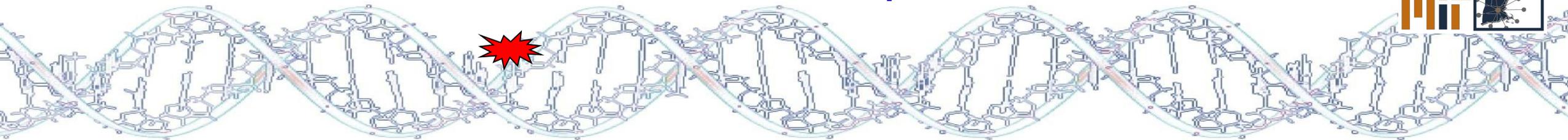


Cells have a Backup Copy = The Opposite Strand

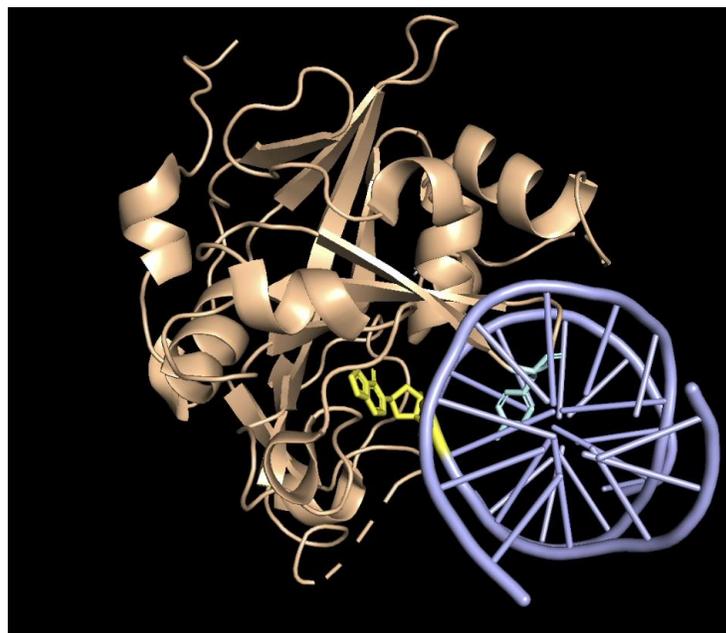
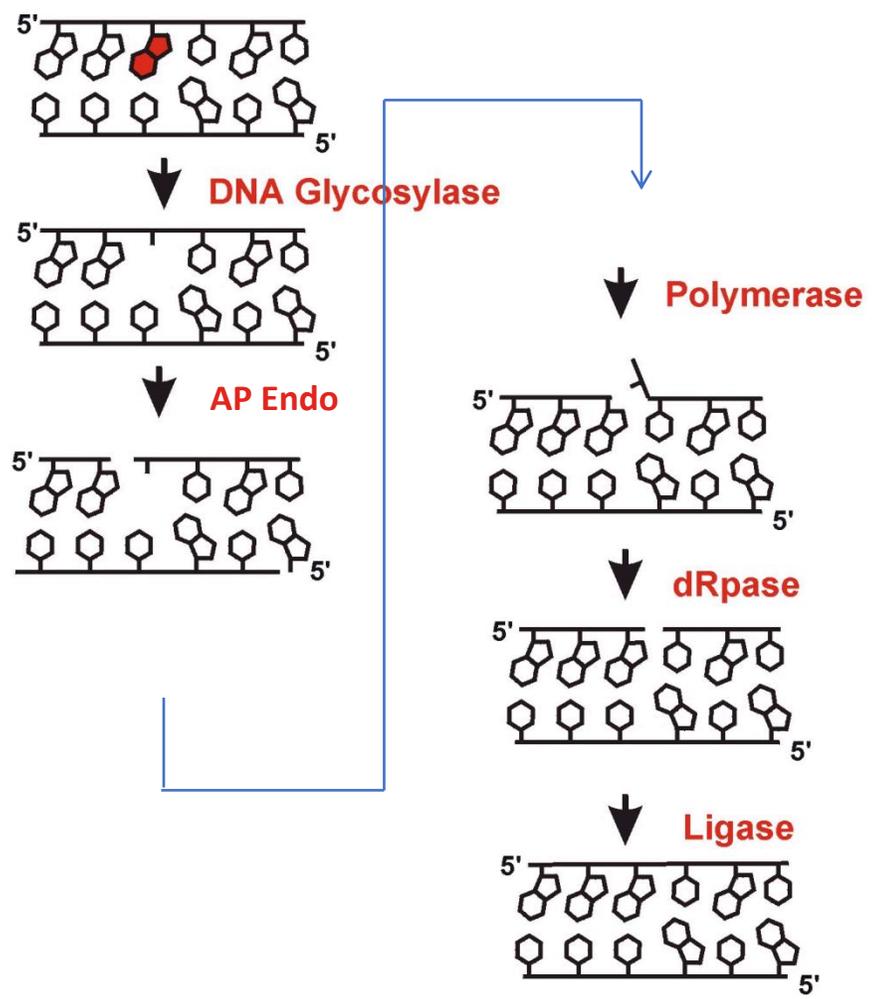


A. Lau, L. Samson and T. Ellenburger; Harvard.

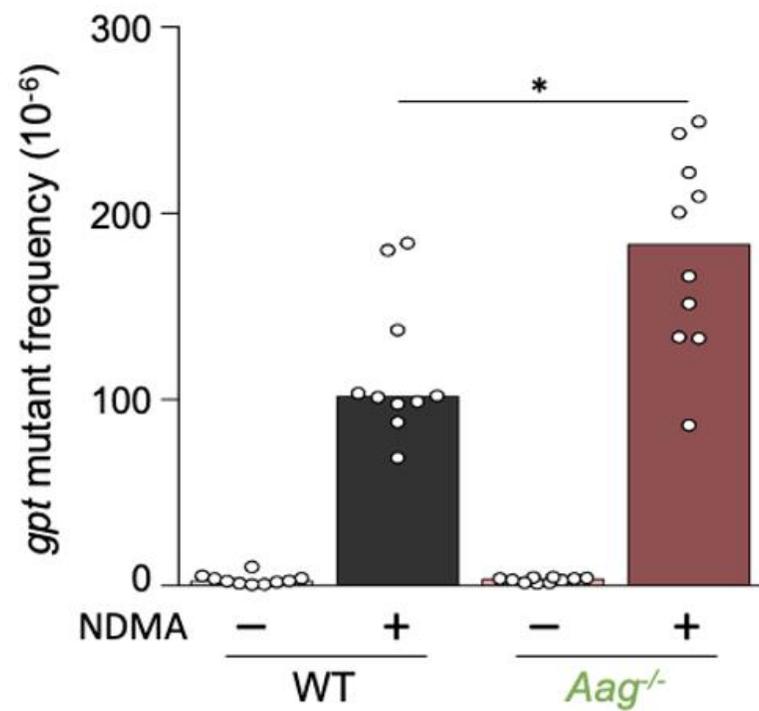
Base Excision Repair



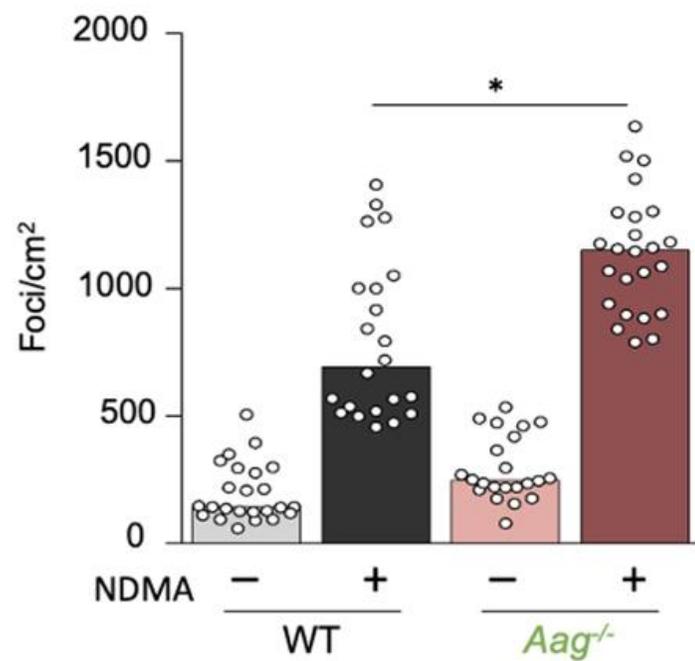
3MeA



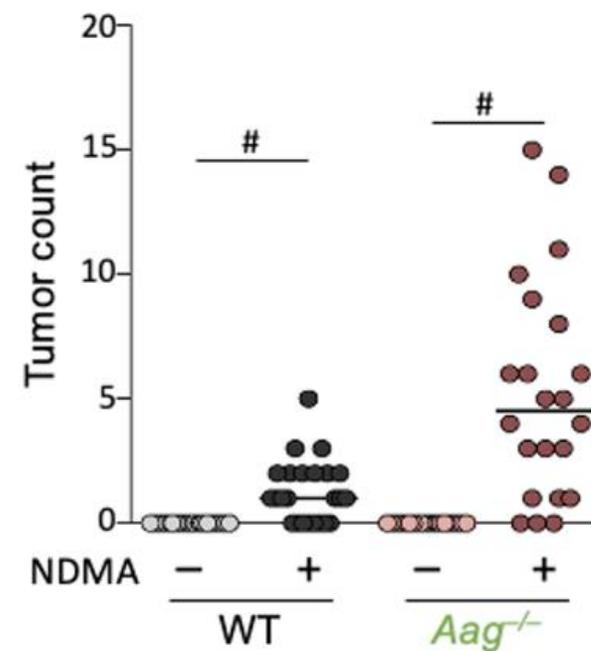
Point Mutations



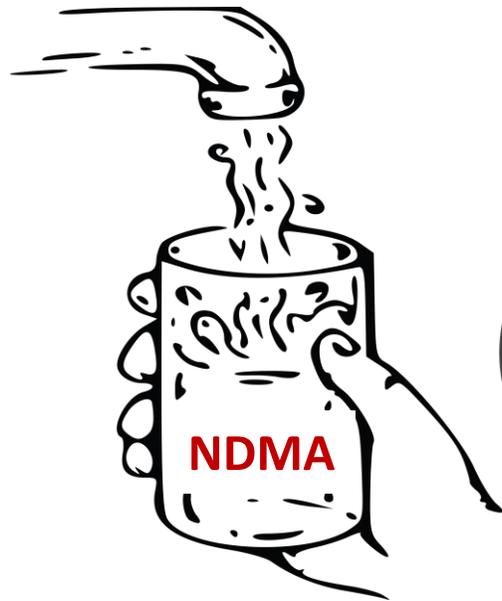
Large Scale Sequence Rearrangements
(Homologous Recombination)



Cancer



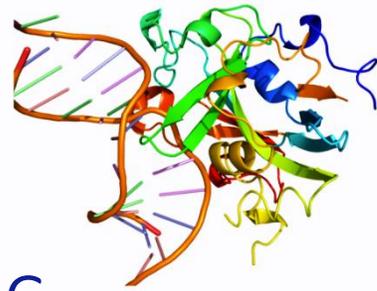
Contaminated
Water near the
Olin Chemical
Superfund Site



→
NDMA
Induced
Mutations

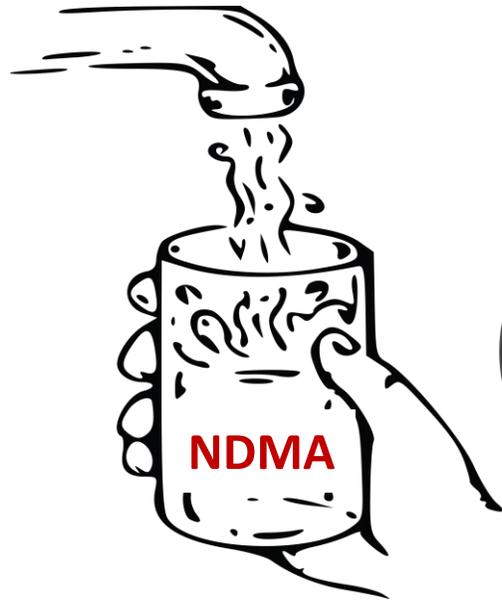


Childhood
Cancer

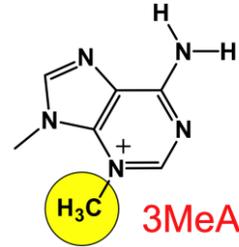


AAG Repair Enzyme

Contaminated Water near the Olin Chemical Superfund Site



AAG
Removal of Mutagenic DNA Damage



Predicted Prevention in People



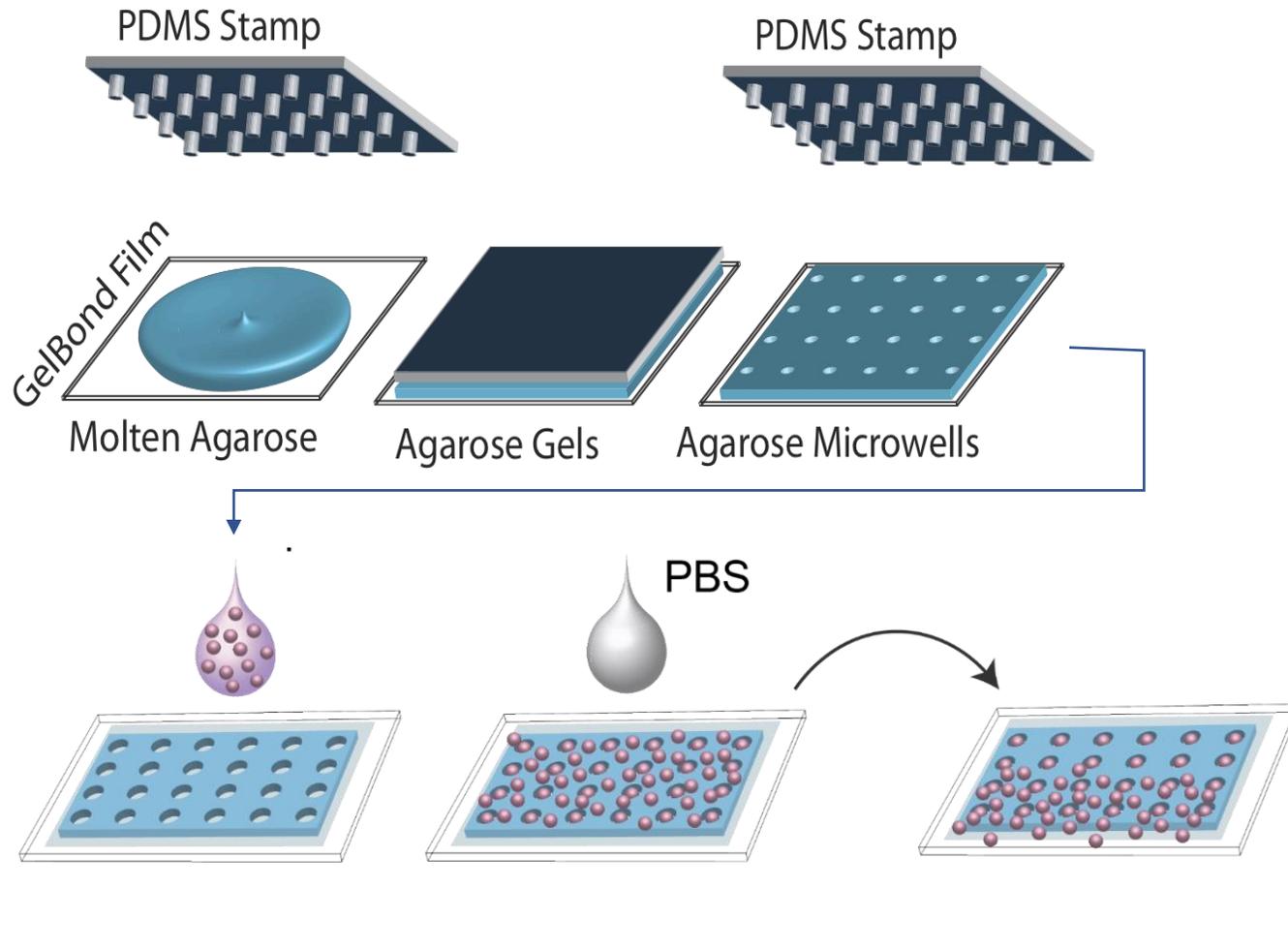
NDMA
Induced Mutations



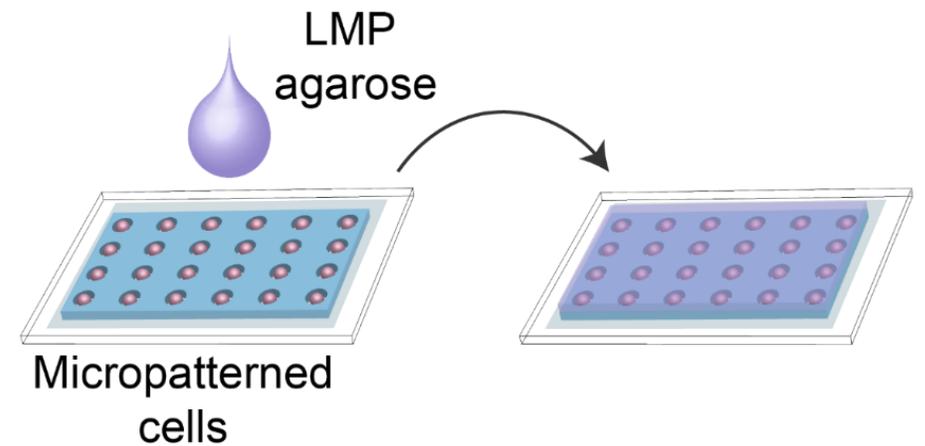
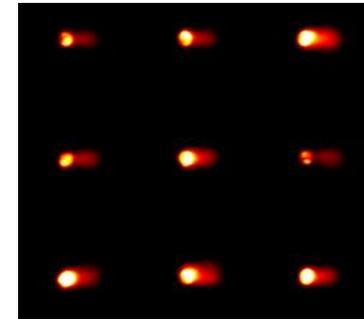
Childhood Cancer

Also Ongoing:
Studies of the impact of probiotics on mutations and cancer.

Different types of Nitrosamines can be studied using the CometChip



Goal: Study the DNA damaging potential and repair responses for multiple *N*-nitrosamines.



Project 2

Trainees:



Amanda Armijo



Bogdan Fedeles
Key Collaborator

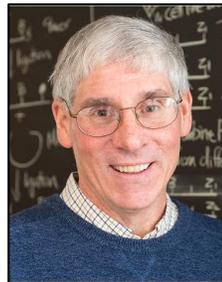


Anna Dormitzer



Nina Gubina

P2 Leaders:



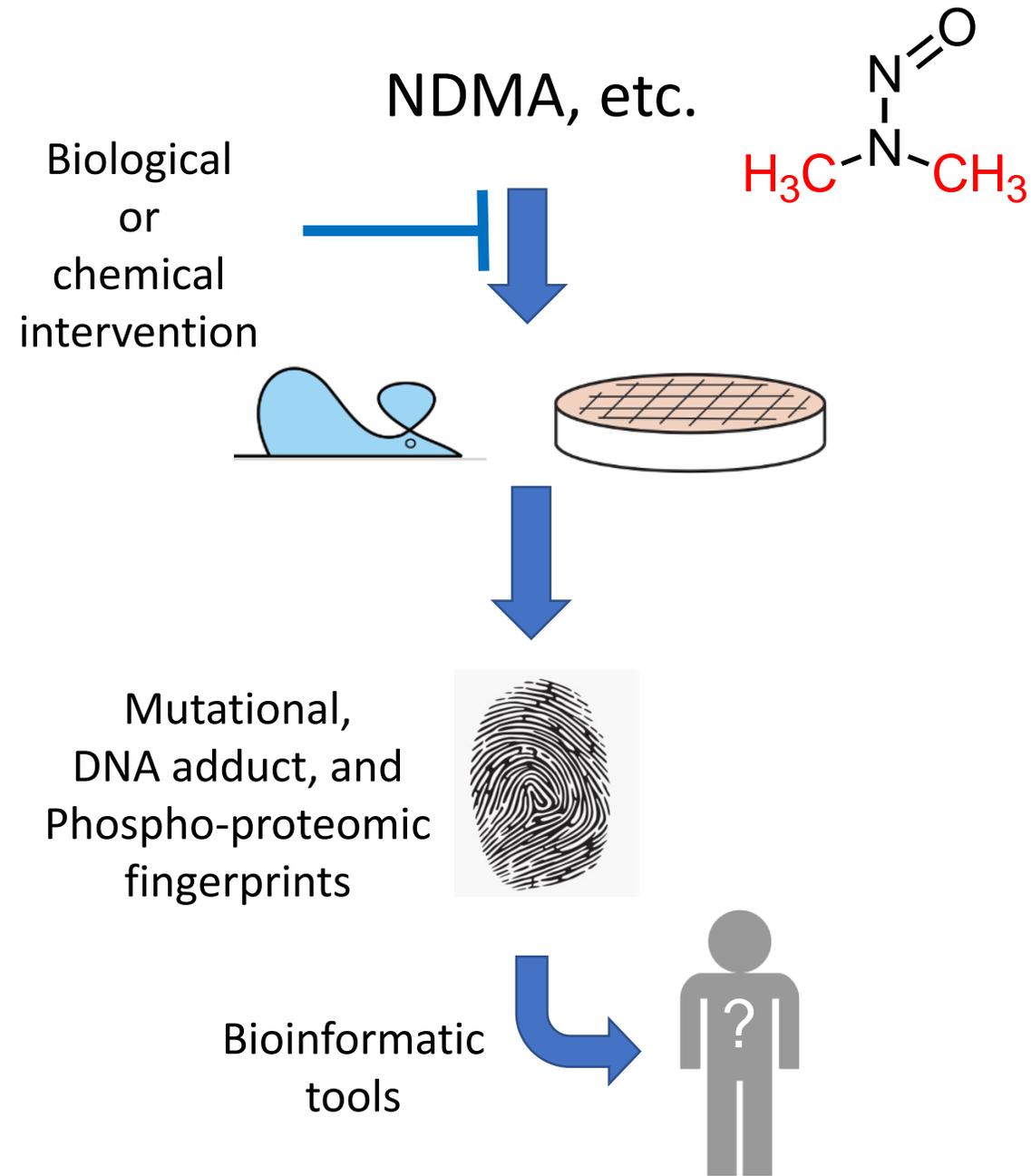
John Essigmann

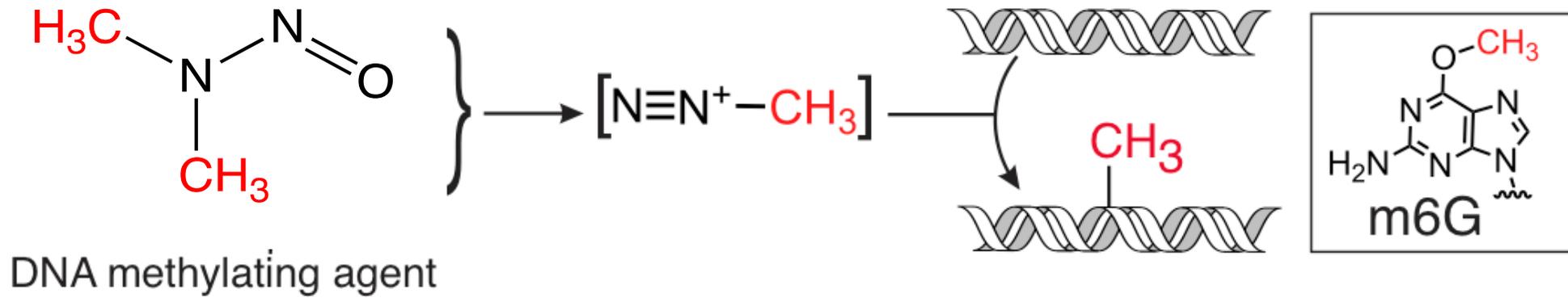


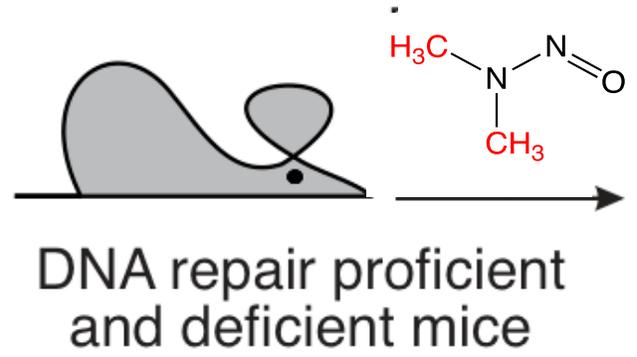
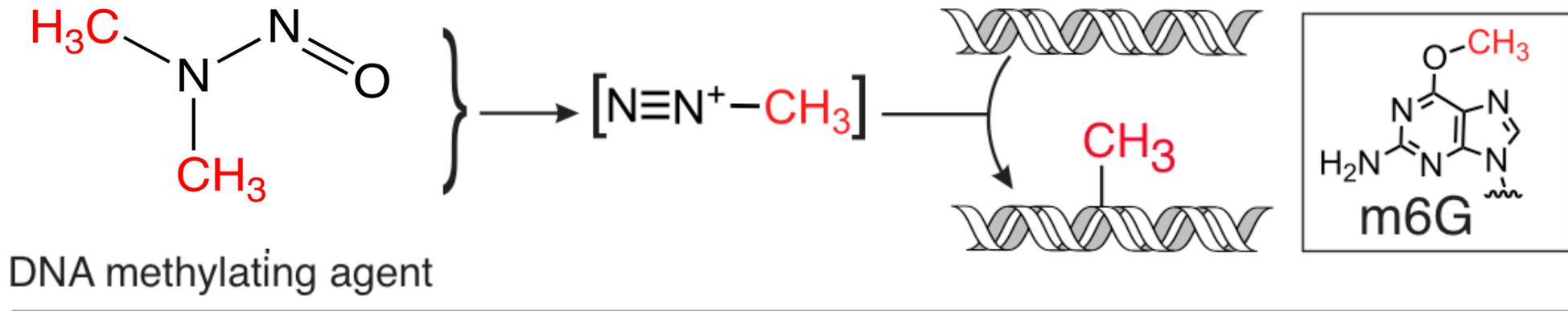
Robert Croy

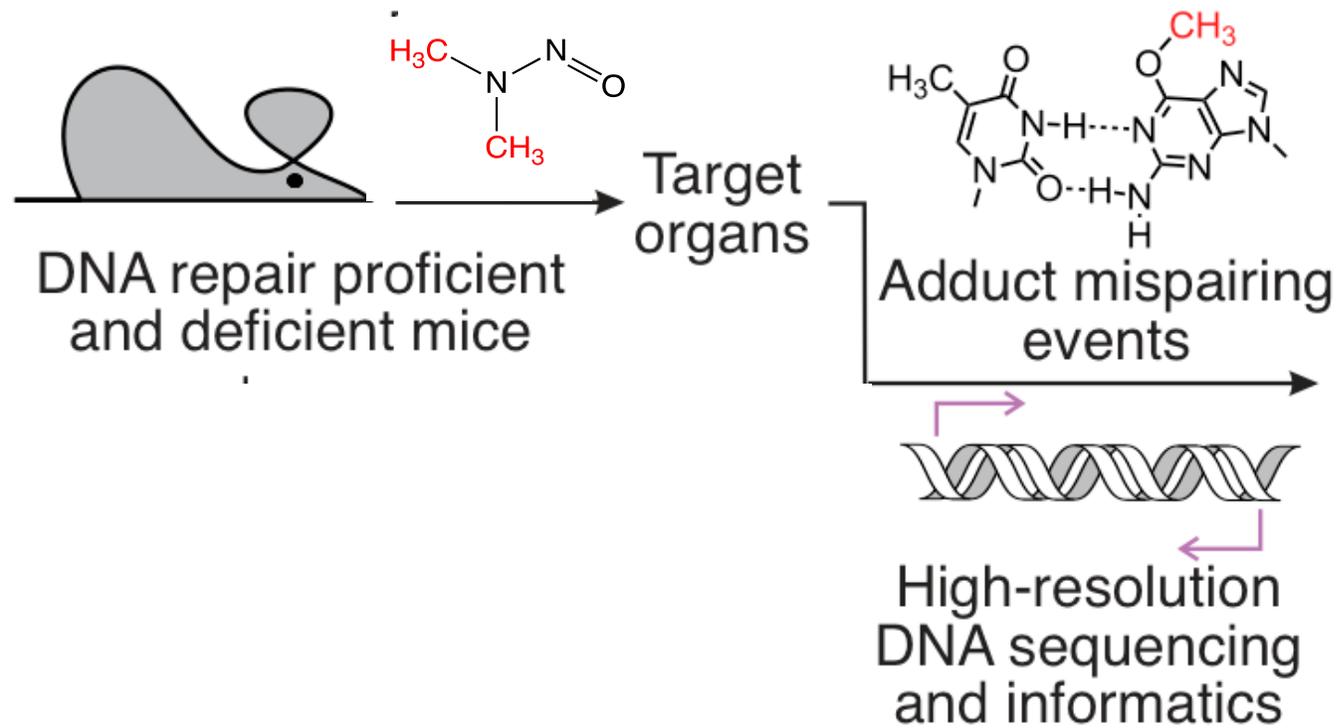
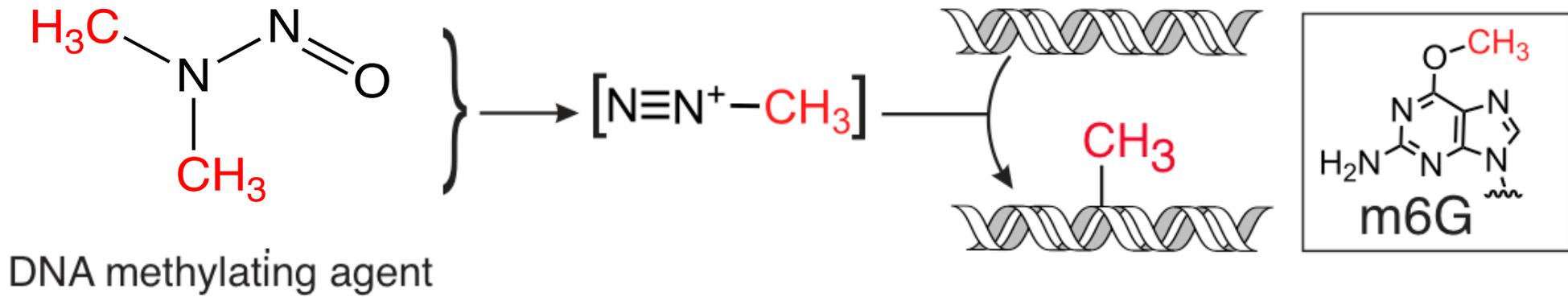


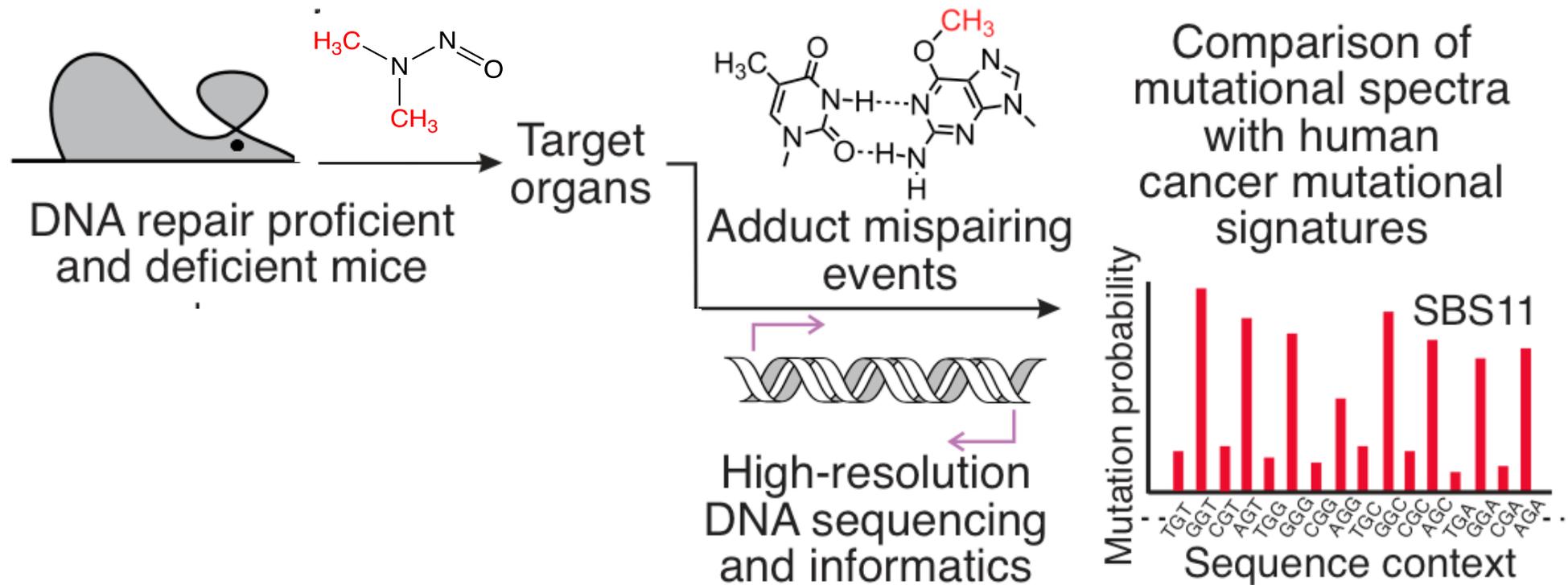
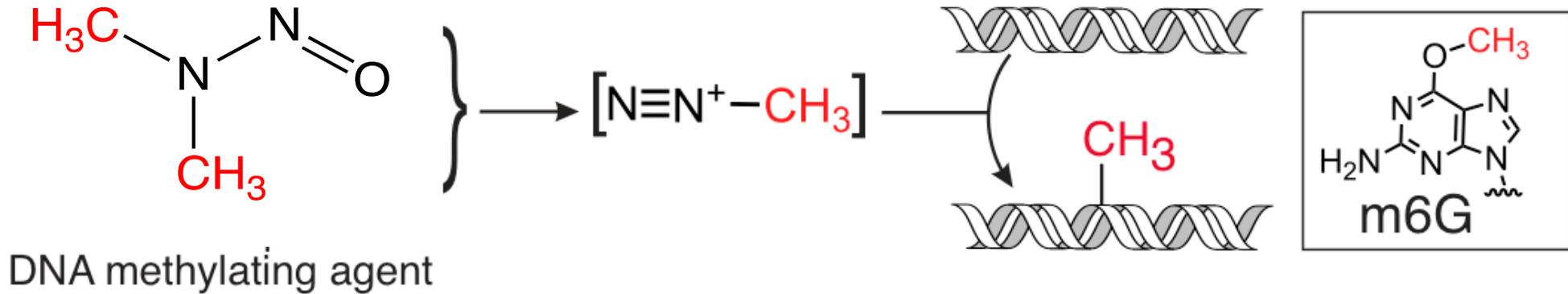
Forest White

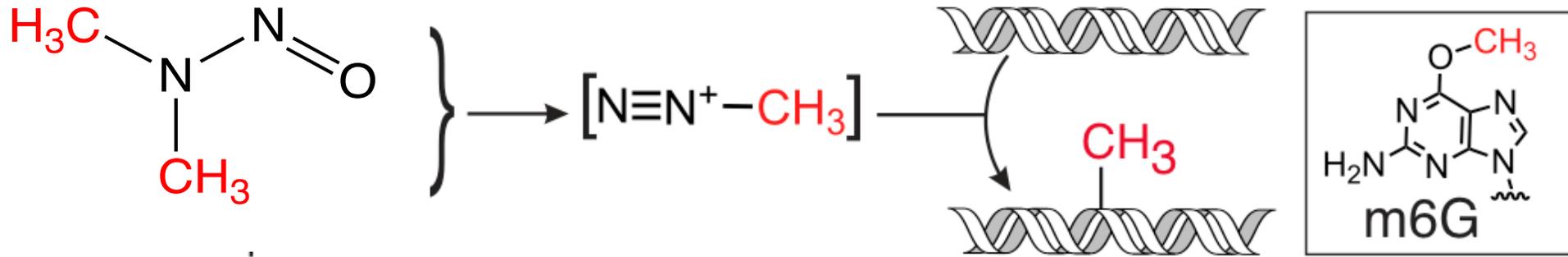




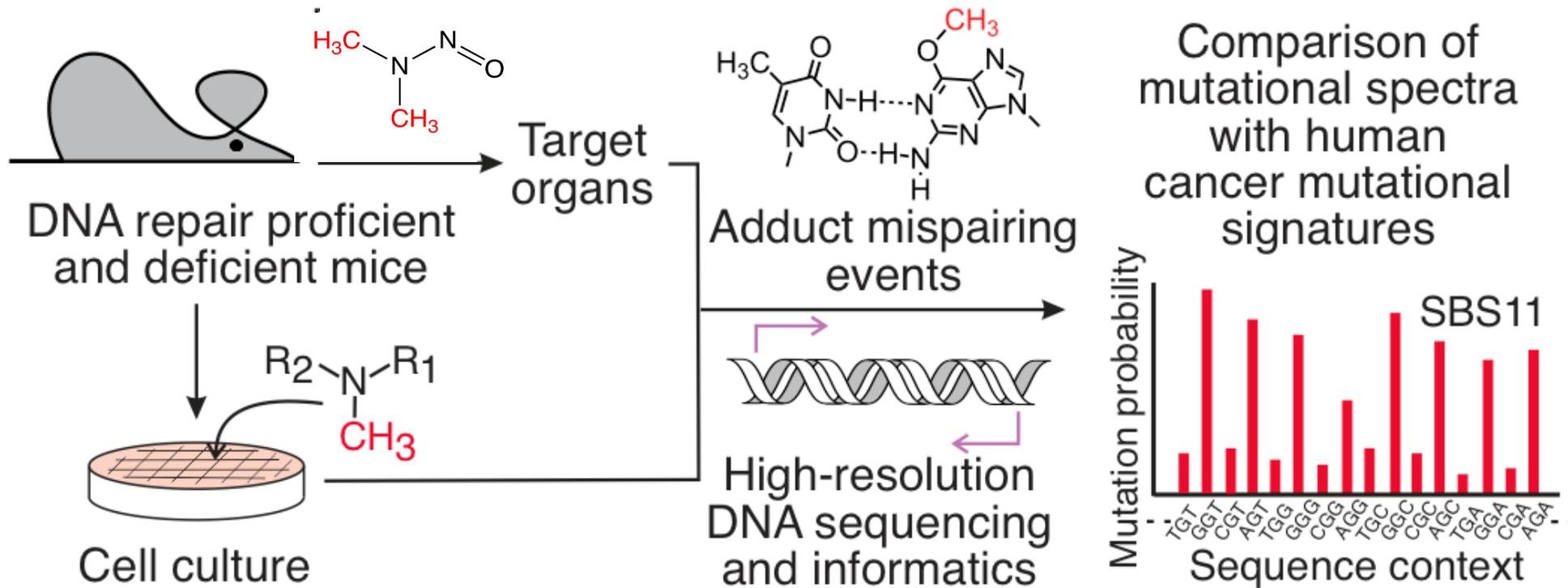


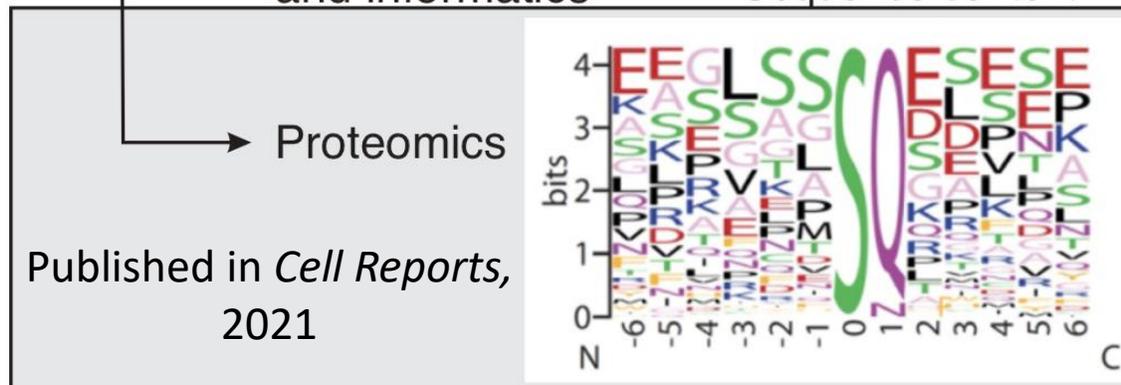
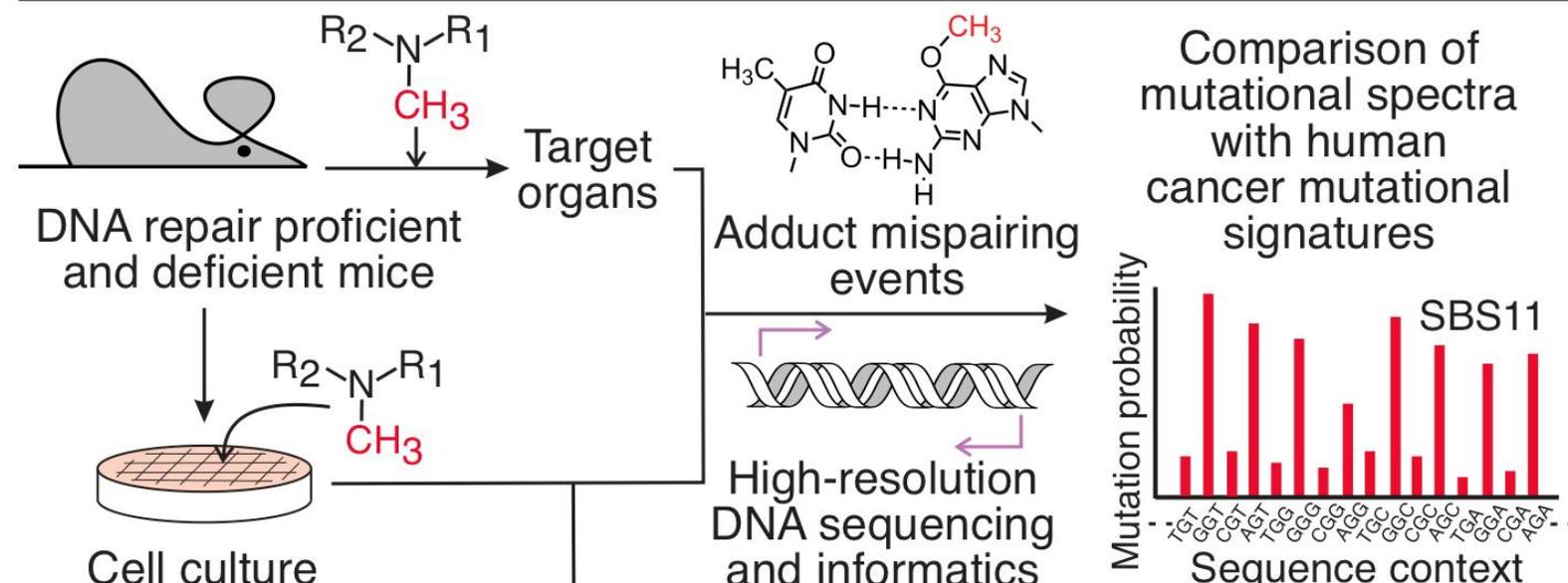
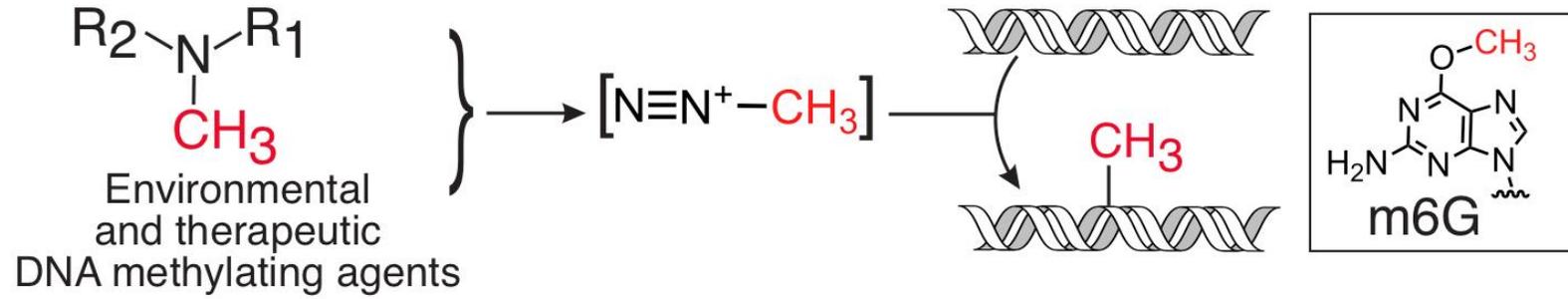






DNA methylating agent





- Mutational pattern could be used to detect prior exposure to NDMA
- DNA adducts (e.g., O⁶MeG) are likely trigger proteomic patterns that explain signaling events in the wake of NDMA exposure
- Proteomic and genomic patterns could lead to precision therapies for NDMA-induced cancers

Project 3

Trainees:



Zhewen Guo



Jessica Beard



Haosheng Feng

P3 Leader:

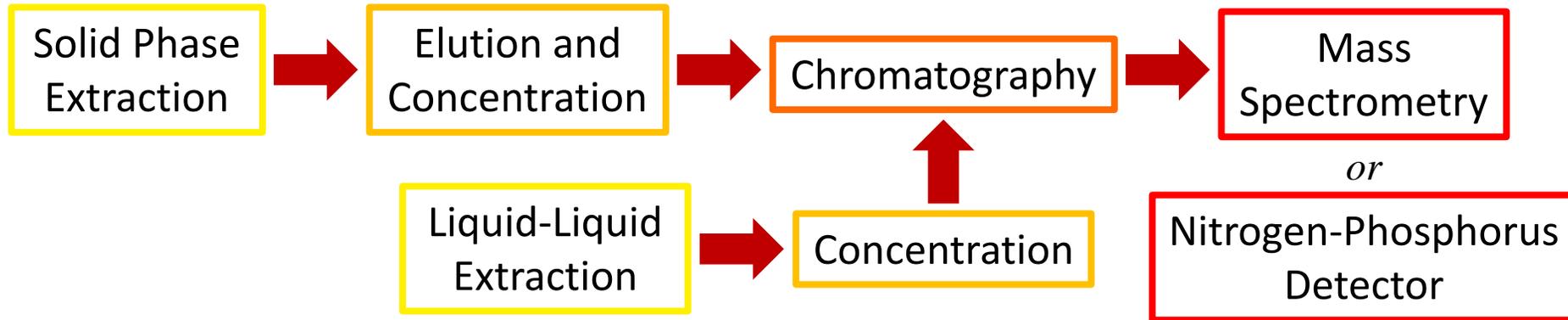


Prof. Timothy Swager

Sensing Nitrosamines in Water

EPA tap water screening level for NDMA: 0.11 ng/L (0.11 ppt)

Most Common:



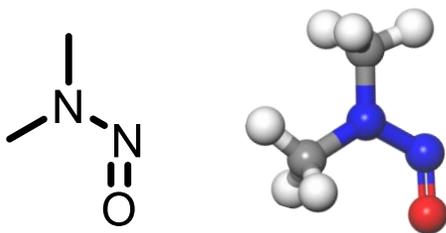
Drawbacks:

- Significant sample prep
- Time-consuming
- Expensive equipment
- Requires skilled personnel

Cannot be used
in-field

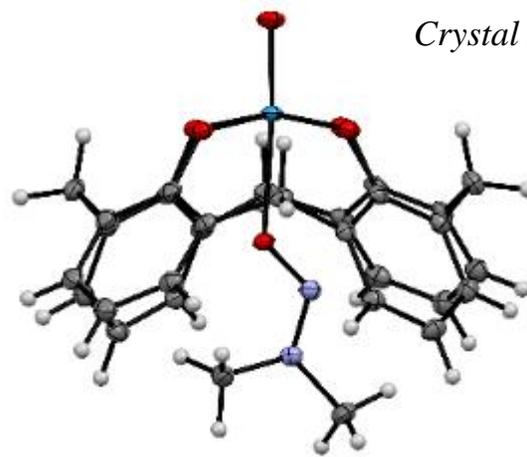
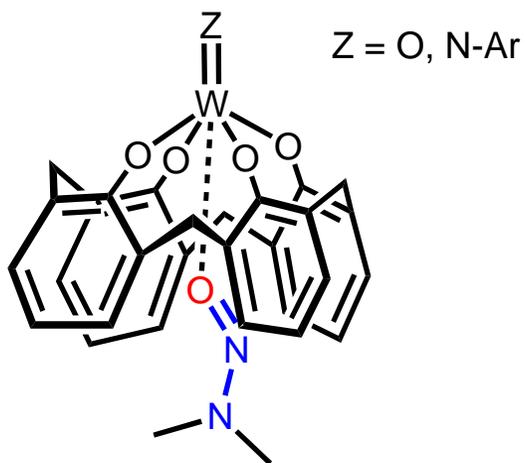
EPA Method 521's LOD for NDMA: **0.28 ppt**

Metallocalixarene NDMA Receptors

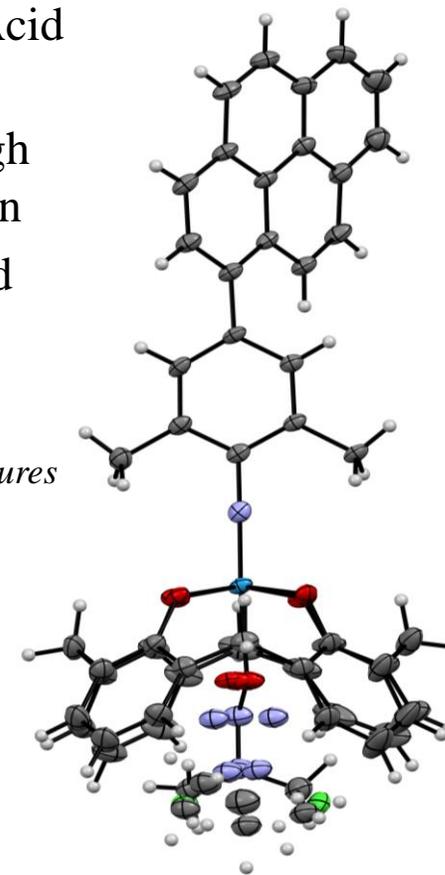


N-Nitrosodimethylamine (NDMA)

- Constrained Endohedral Lewis Acid Structure
- Ideal for Binding NDMA Through the Lewis Basic Terminal Oxygen
- Multiple Examples Characterized by X-ray Crystallography

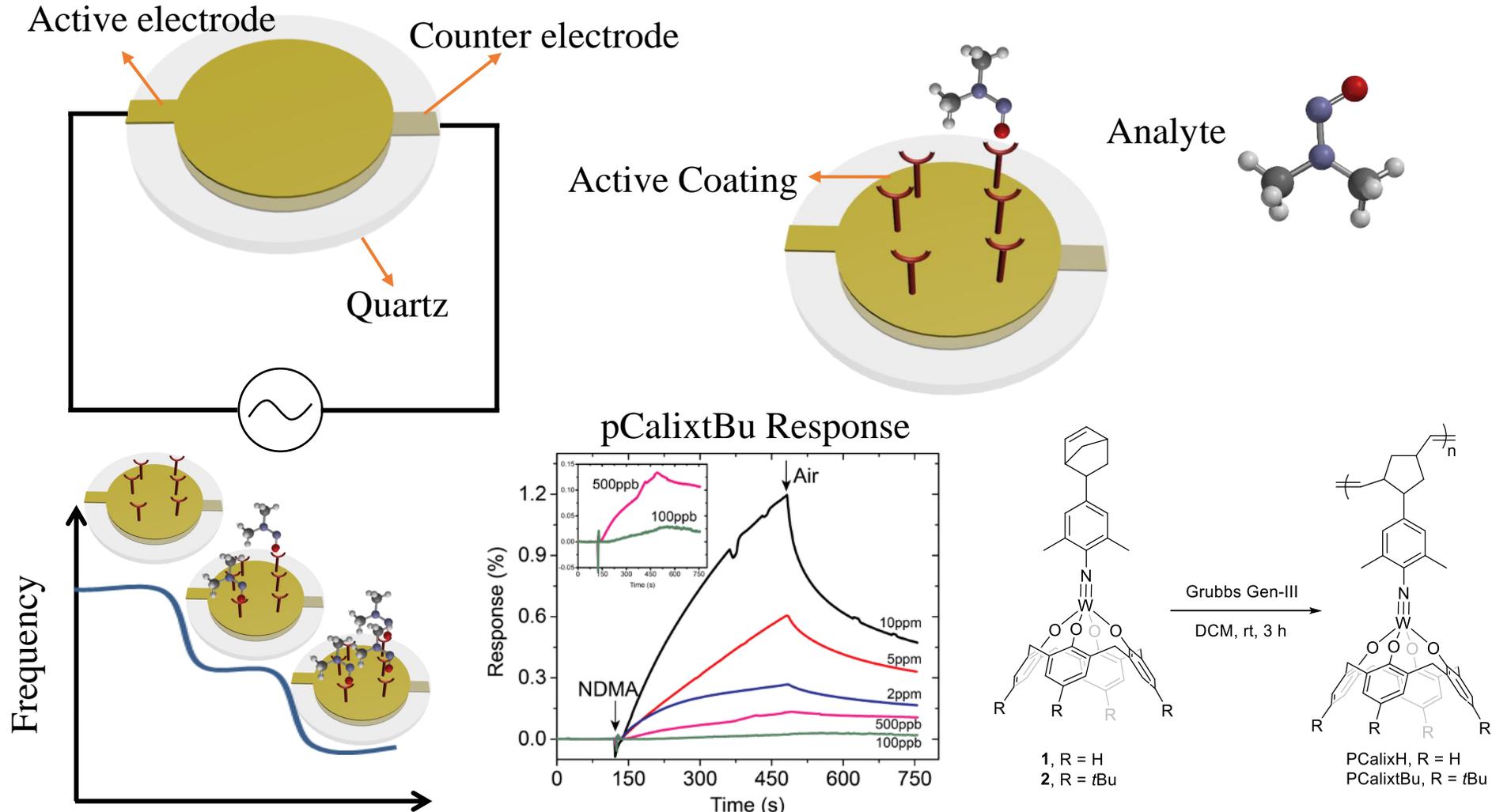


Crystal Structures



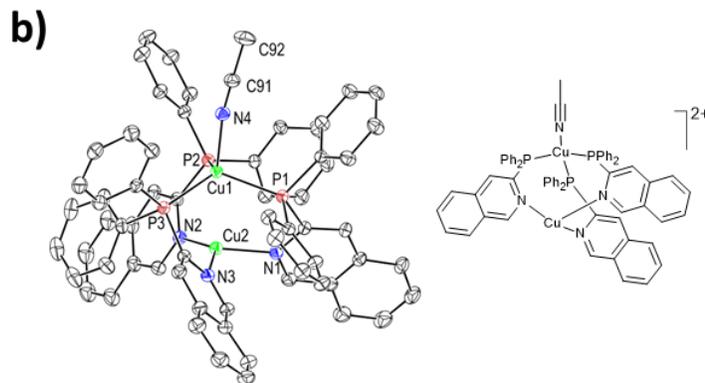
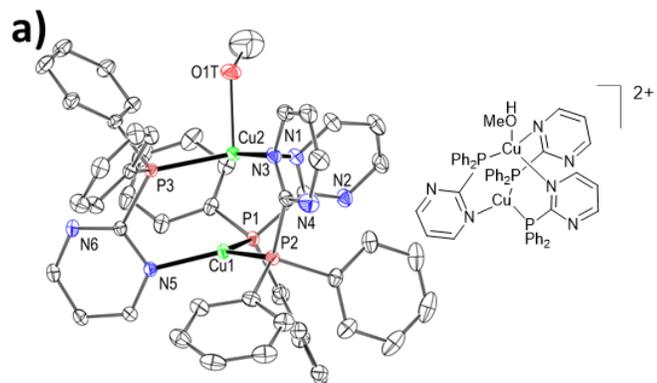
NDMA Detection

Quartz Crystal Microbalance (QCM)

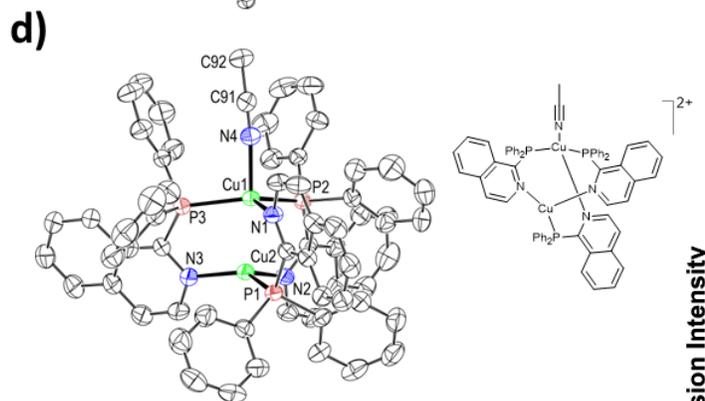
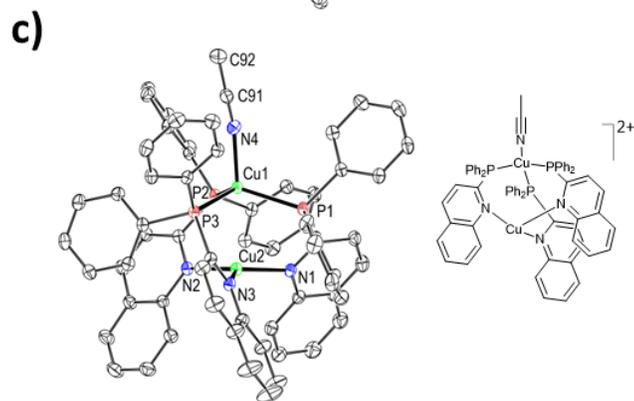


Lu, R. -Q.; Yuan, W.; Croy, R. G.; Essigmann, J. M.; Swager, T. M. "Metallocalix[4]arene Polymers for Gravimetric Detection of *N*-Nitrosodialkylamines" *J. Am. Chem. Soc.* **2021**, *143*, 19809-19815.

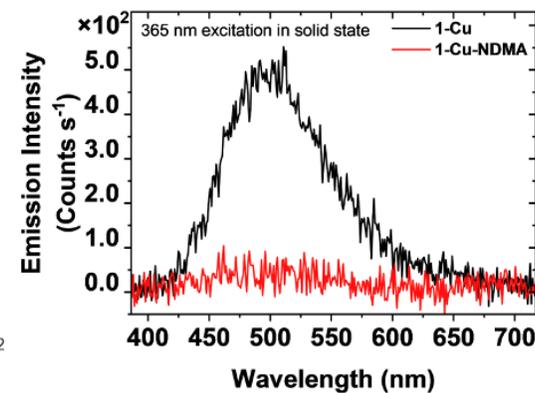
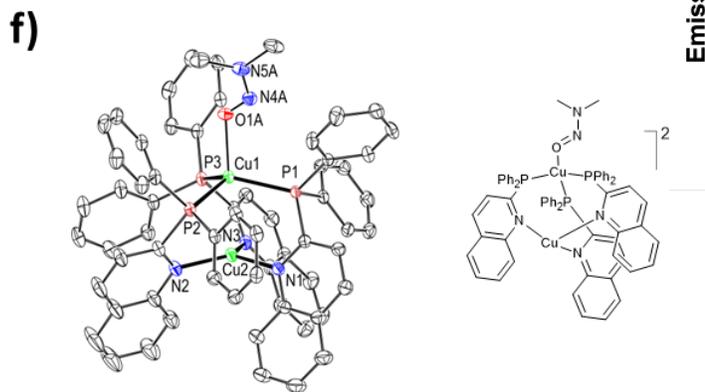
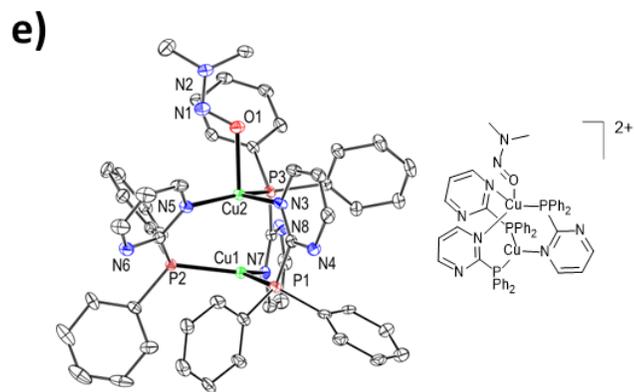
Luminescent Sensors with NDMA Triggered Quenching



Metal Complexes for NDMA Binding based on Cu^{+1} Paddlewheel Structures



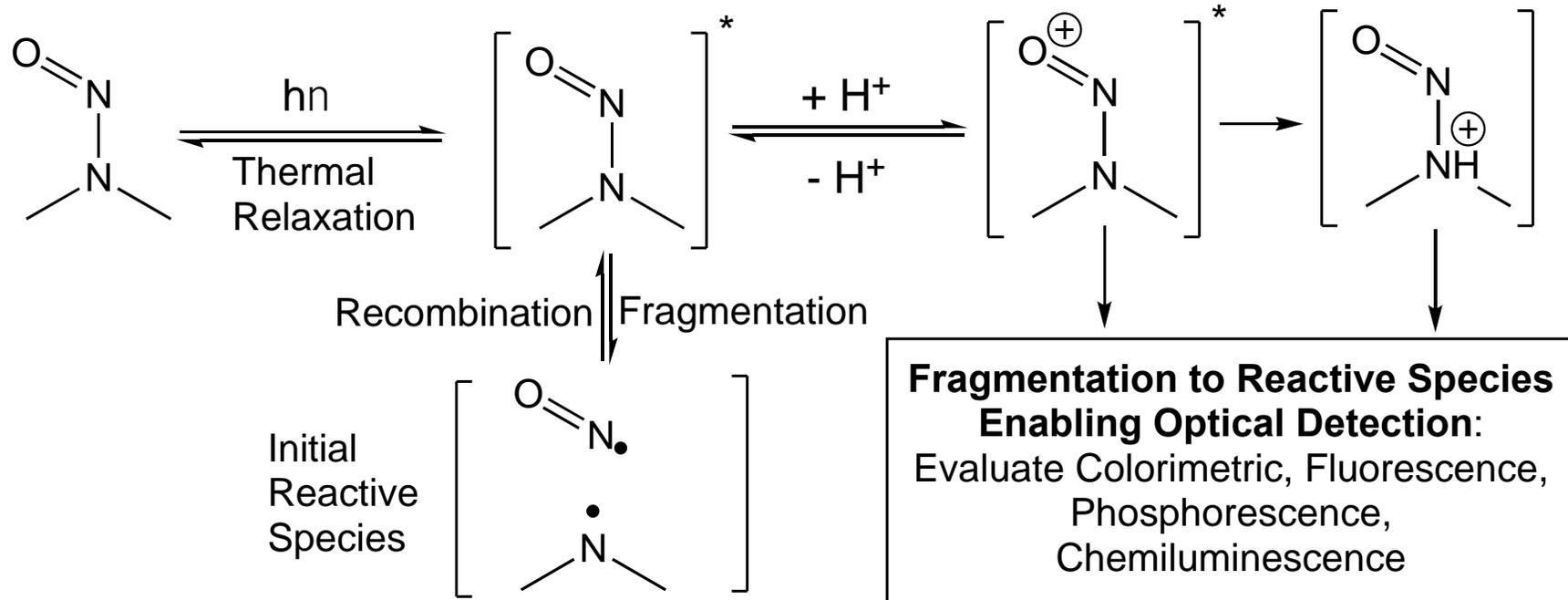
Limit of Detection 2.8 ppm



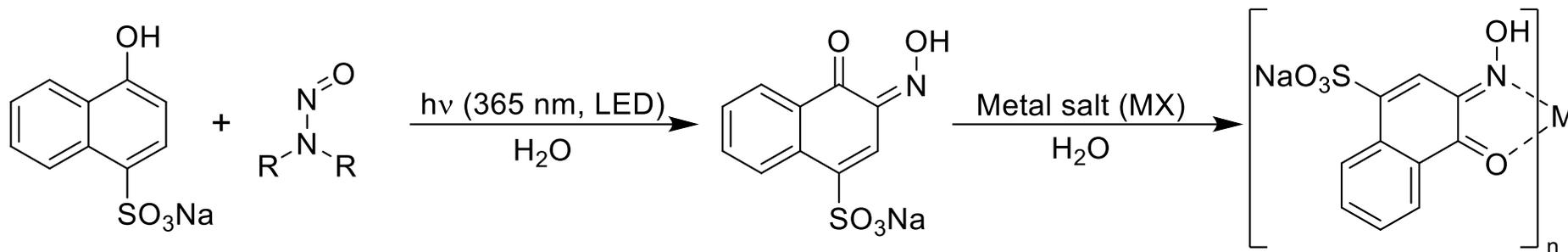
Multiple Complexes Characterized

NDMA Chemistry is the Key to Other Detection Methods

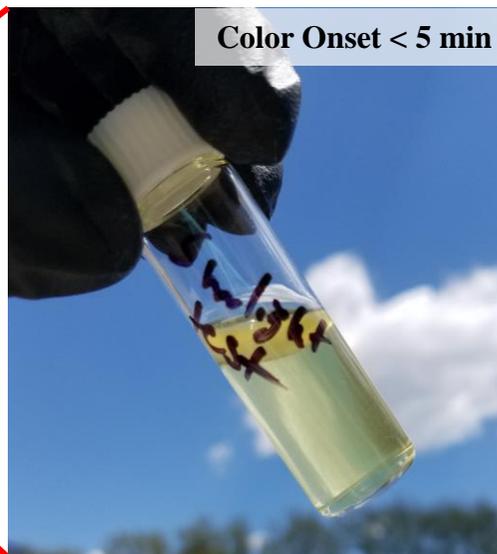
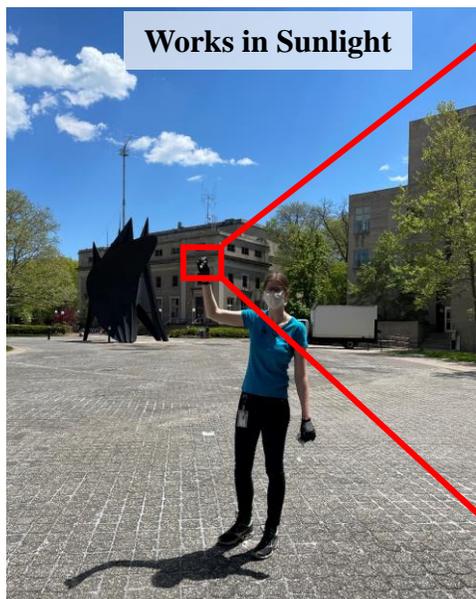
Leverage the Photochemical Reactivity of NDMA and Related Species



Optical Methods for NDMA Detection



Photoacid Facilitates
Electrophilic Addition by NO⁺



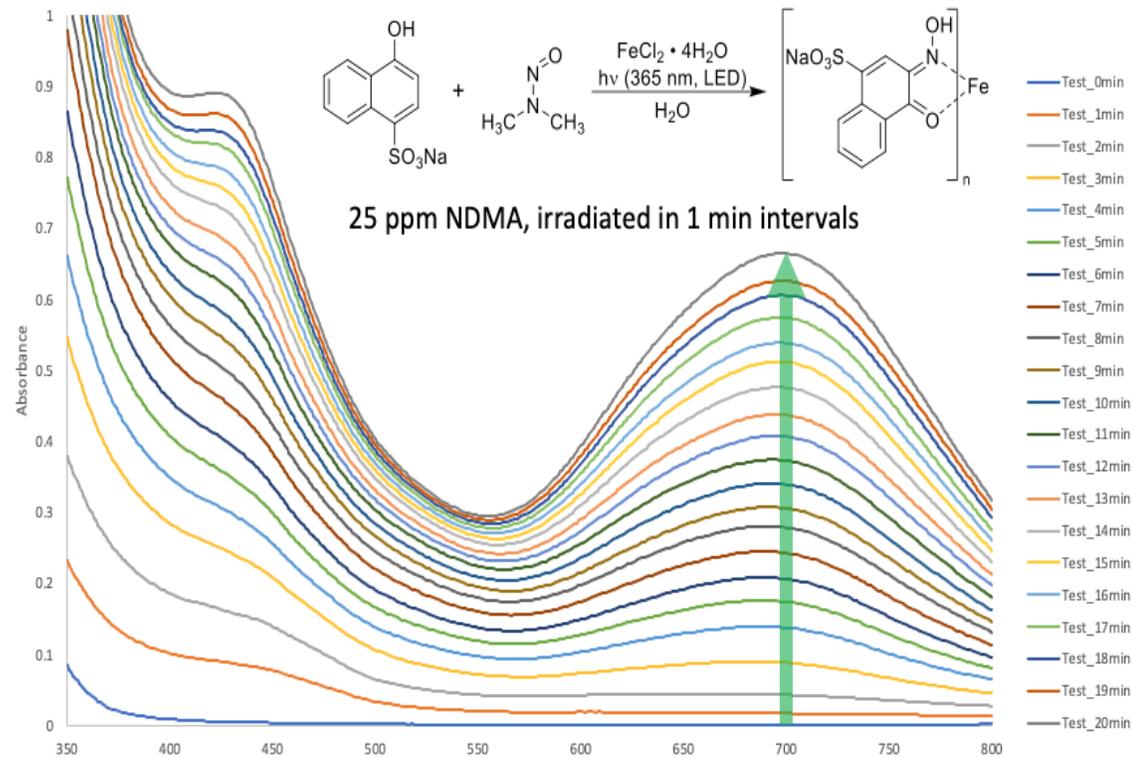
Metal Salts for Enhanced Color



Jessica Beard

Improved NDMA Detection by Concentration of Products

Formation of Iron Complex *in situ*

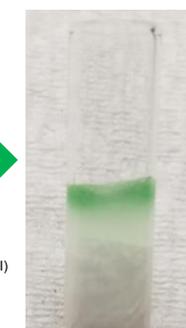
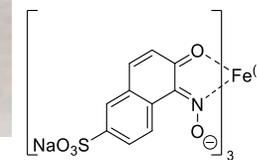


Concentration on Supports Improves Sensitivity



9.5 μ M Naphthol Green B

Pass through plug of Dowex 1 \times 2 chloride form resin beads

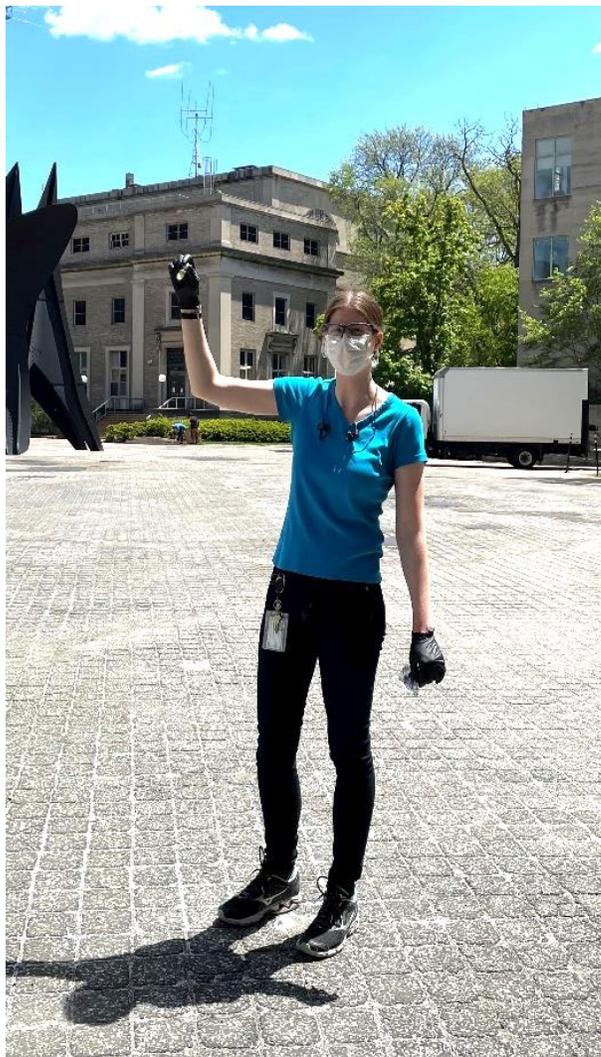


Naphthol Green B

Jessica Beard

No LED? No Problem!

Reaction works under sunlight!

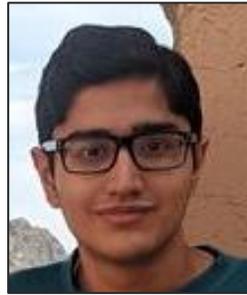


250 ppm NDMA, MilliQ water

Jessica Beard

Project 4

Trainees:



Barath Baskaran

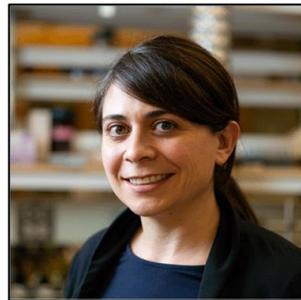


Kristen Riedinger



Nicolette Bugher

P4 Leaders:



Prof. Desiree Plata



Prof. Ariel Furst

Relevant exposures?

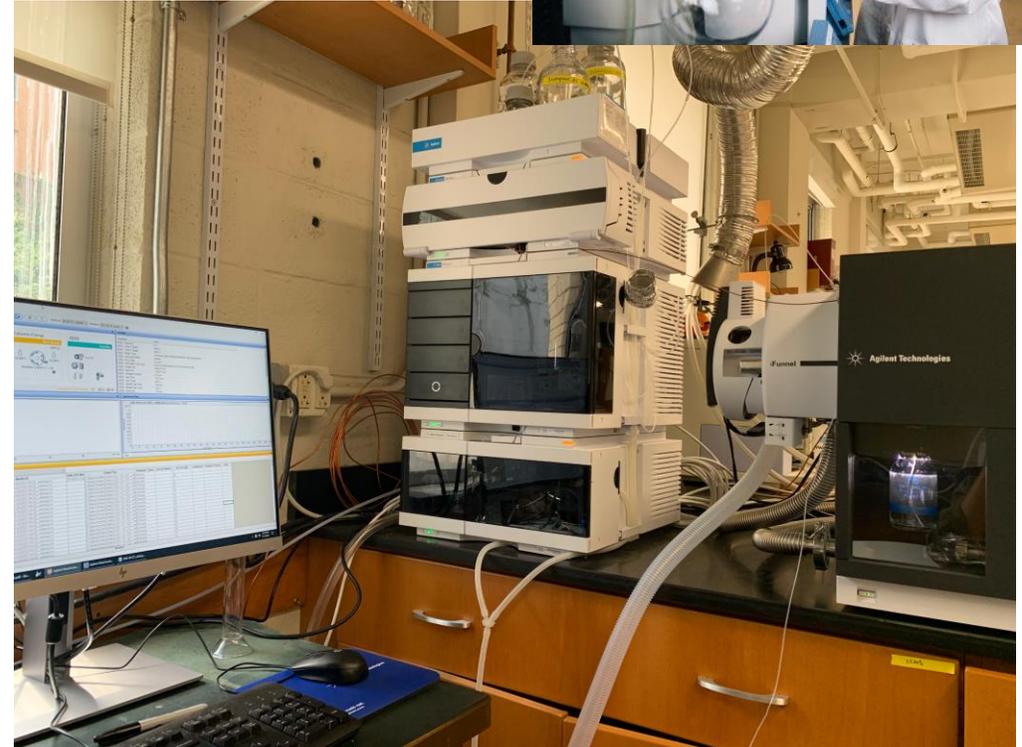


Analytical improvements

Solid phase extraction



LC-QQQ-MS

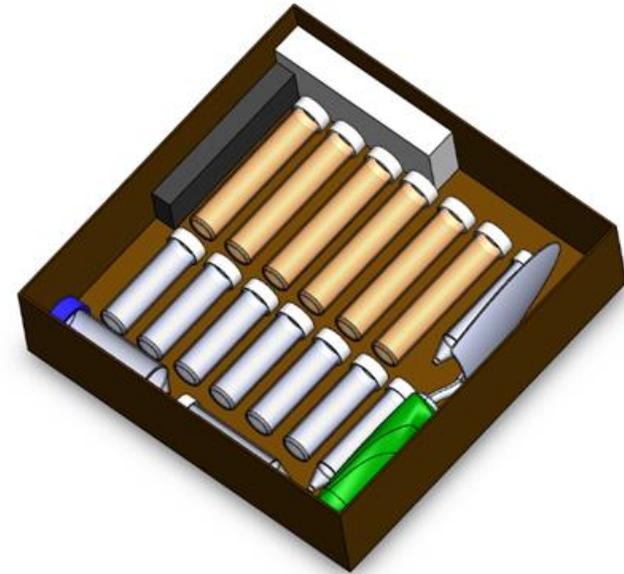


Ancillary analysis

P&T-GC-ECD/FID

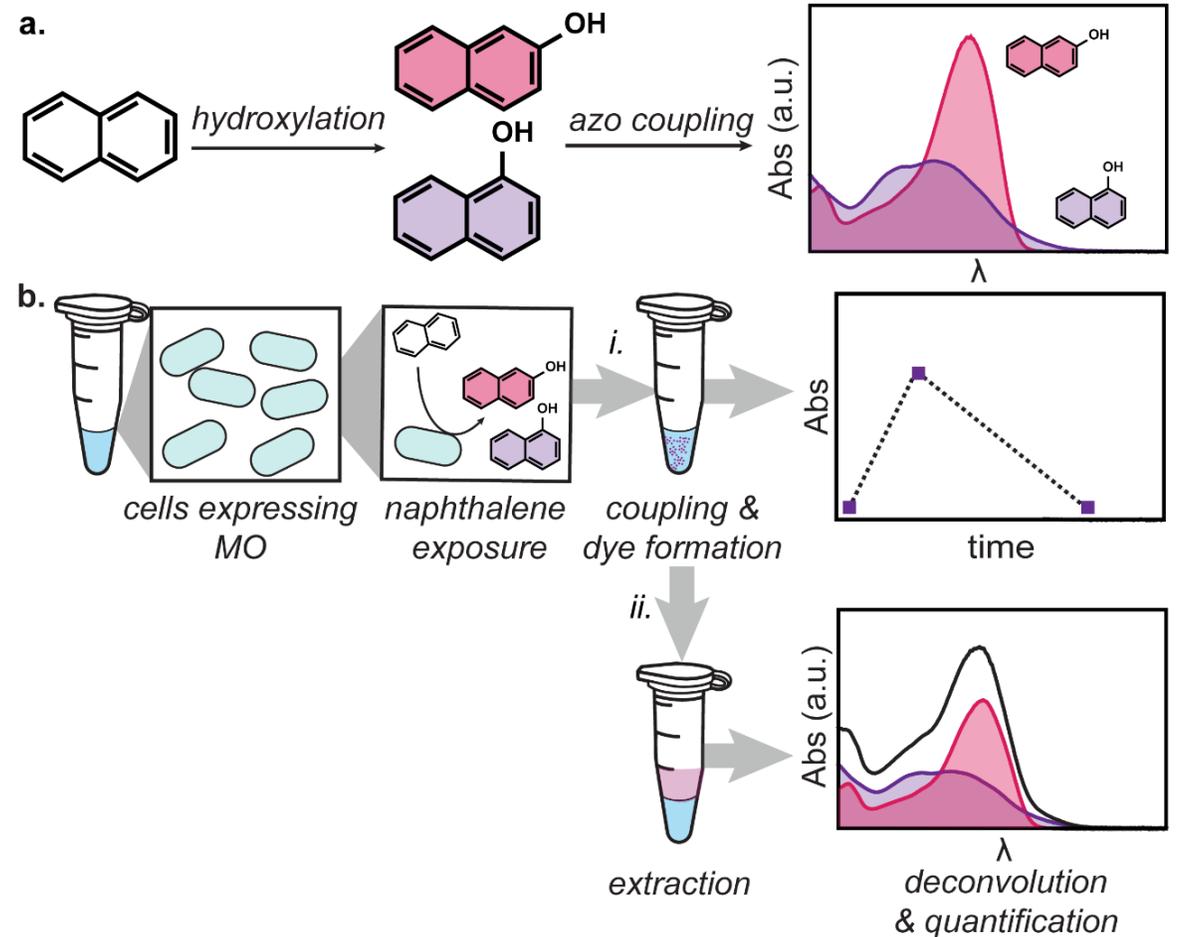
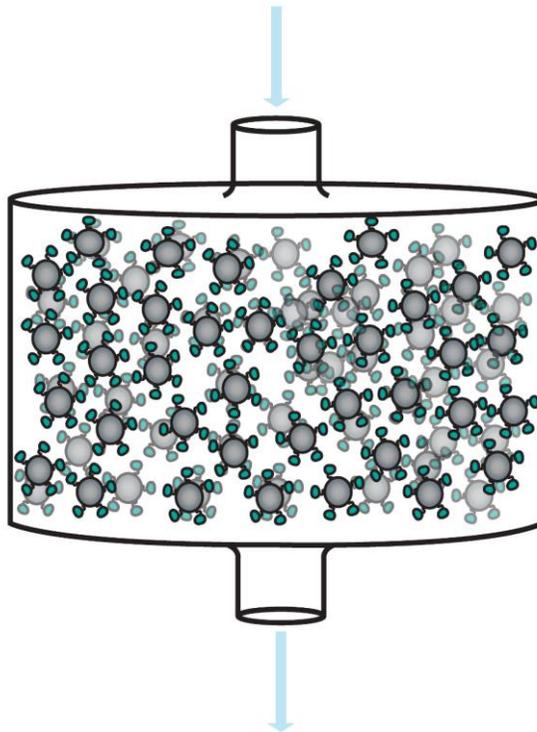


Mail and field kits for expanded sampling



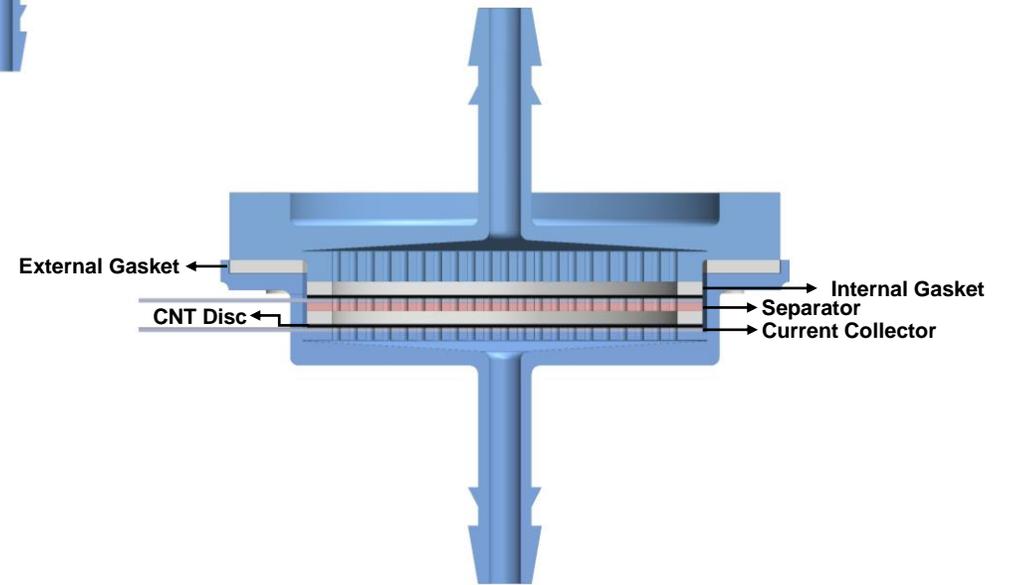
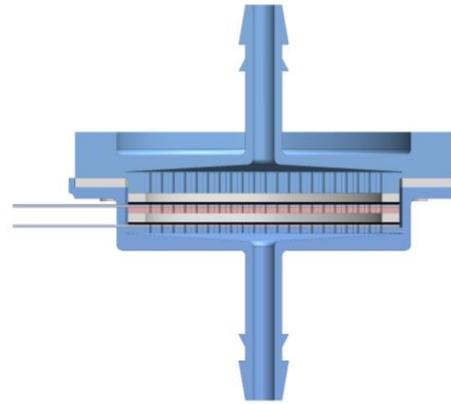
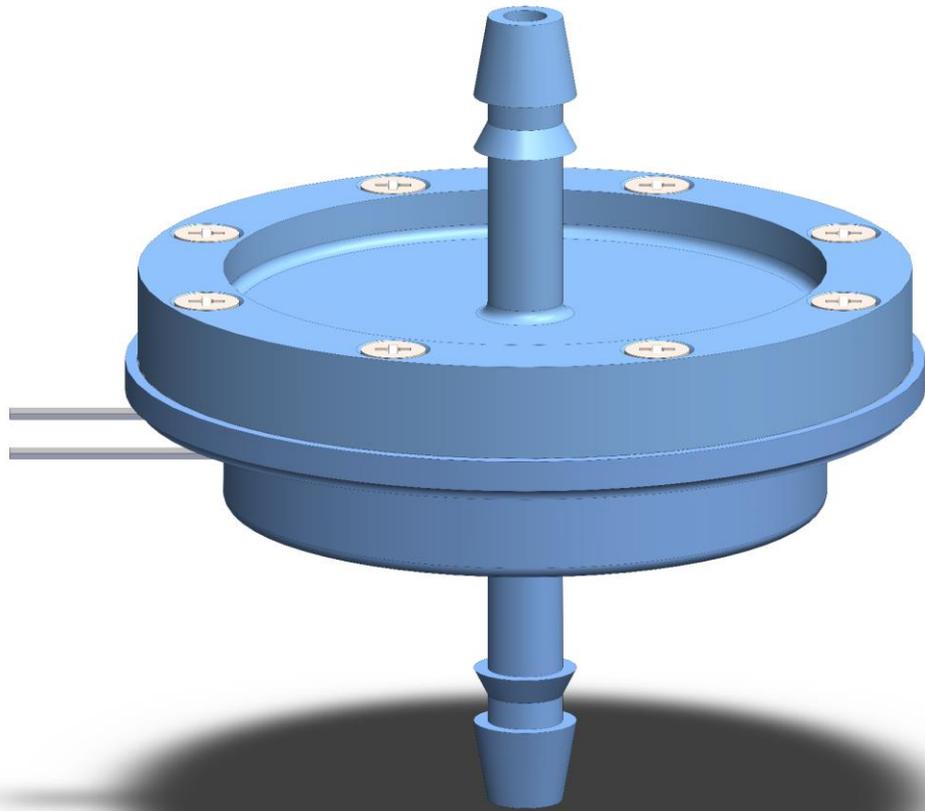
Novel water treatment technologies

Approach 1:



Novel water treatment technologies

Approach 2: Electrochemistry



Novel water treatment technologies

Approach 2: Electrochemistry (cont):



Motivation for Focus on *N*-Nitrosamines
Communities we Learn from and Support
How NDMA Damages the Genome

Mission

Projects

Cores

Team

Our Systems Approach

Administrative Core

Dir. Bevin Engelward
Deputy Dir. Desiree Plata
Deputy Dir. John Essigmann
Tori Hile
Amanda Tat



Tori Hile

Data Management and Analysis Core



Stuart Levine



Forest White



Doug Lauffenburger



David Steinsaltz

NEXtSEEK

Data Analysis

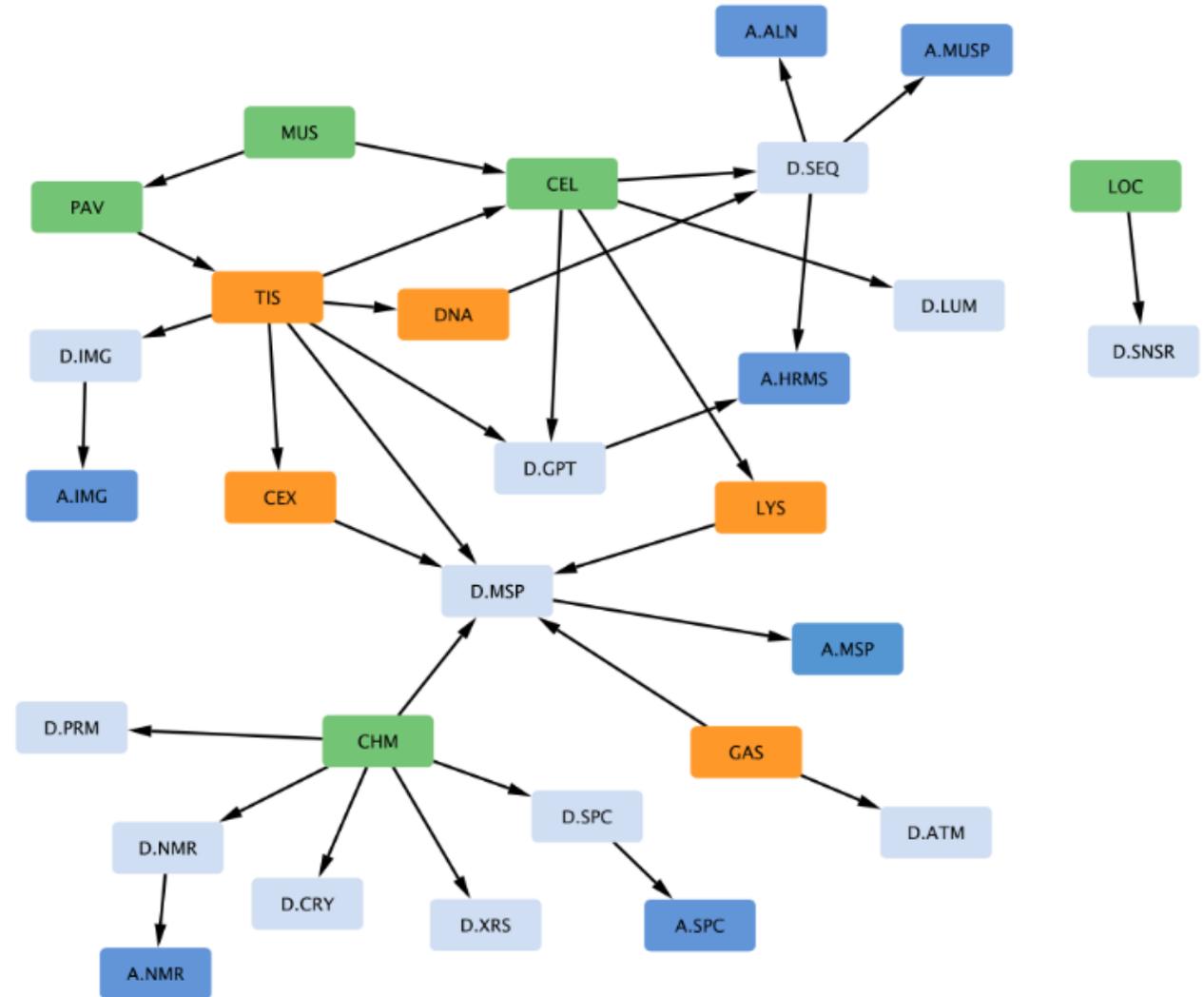
Novel analysis methods
have been shared (Workshops)

Data Management: NEXt SEEK

Metadata for thousands of
samples have been documented
(Who, What, Where, When)

Dozens of protocols
have been linked (How)

Dozens of data sets
have been shared (FAIR)



Network Extended SEEK

Community Engagement Core



Dr. Kathy Vandiver



Dr. Christa Wright

PRESS RELEASE

State Study Suggests Link Between Elevated Rates of Childhood Cancer in Wilmington in the 1990s and Formerly Contaminated Public Water Supply

Childhood cancer incidence returned to expected rates beginning in 2001;
DPH to continue monitoring

March 2021

Cleanup is Underway, but Community Members
Remain Concerned



Wilmington Resident who
had cancer:
“This study makes it possible to do
better going forward.”

“Lessons Learned along the Road to Environmental Cleanup”

Assists All Stakeholders: Community, Government, and Industry

Online Interactive Guide Provides Advice on How to Work Together

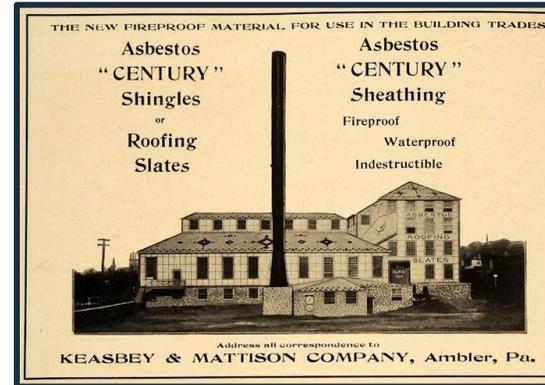


This is a Tale of Three Cities as told by the stakeholders.



1) Wilmington, Massachusetts

**Nitrosamines in
Contaminated Water**



2) Ambler, Pennsylvania

**Asbestos in
Contaminated Soil**



3) Fernald, Ohio

**Uranium in
Contaminated Air**

Susan Pinney (U. Cincinnati P30 ES006096)

Marilyn Howarth (U. Penn P30 ES013508)

Kathleen Vandiver (MIT P42-ES027707)

CEC Director annually attends EPA Region 1 Tribal Environmental Conferences

Culture Keepers (tribal educators) share traditional knowledge and values
with members of the MIT SRP and the EPA Region 1



Sipayik Tribal Men Big Drum – includes Tribal youth

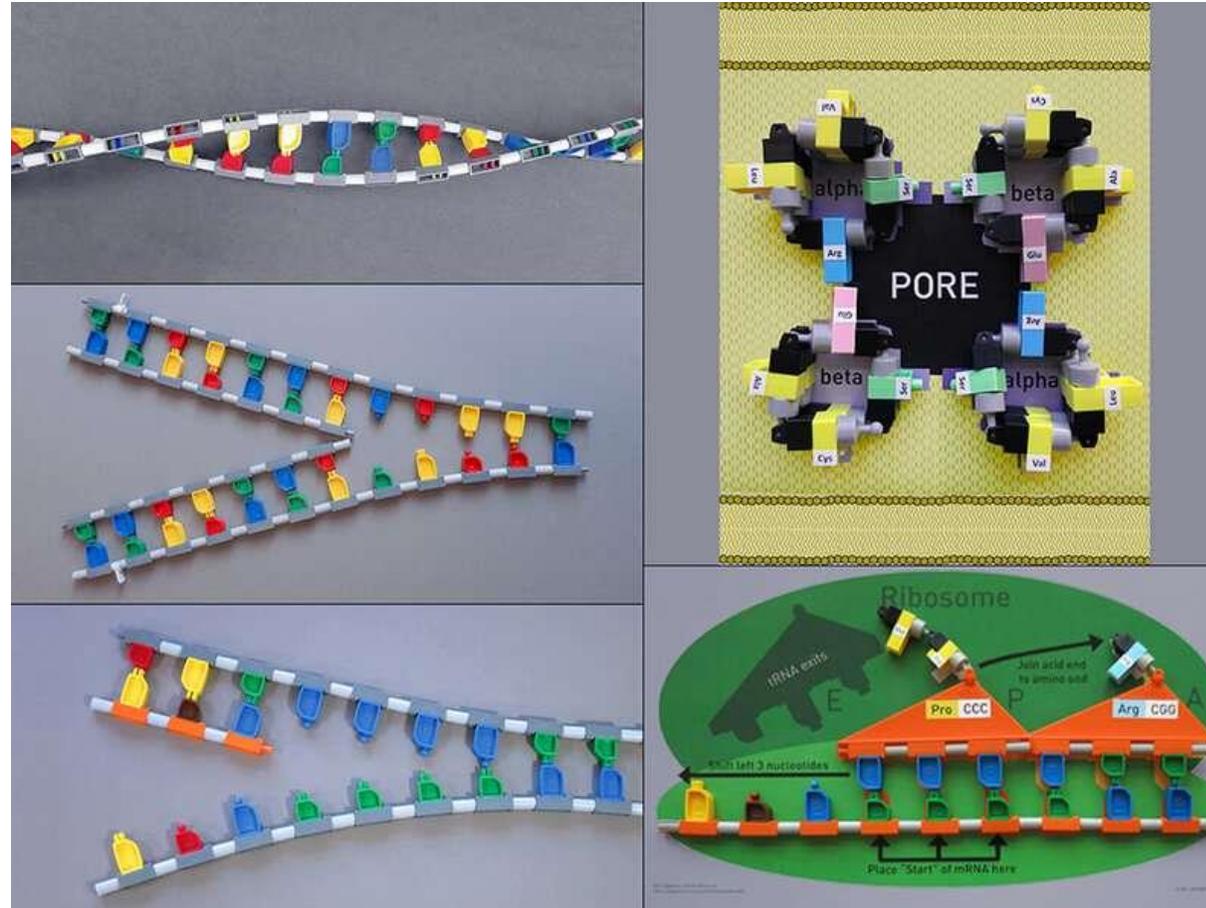


Gathering Sweetgrass for making Traditional Baskets

Bidirectional Education with the Passamaquoddy Tribe

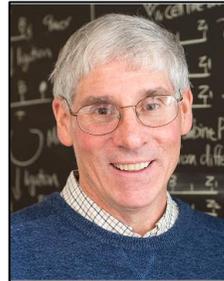
CEC collaborates with Culture Keepers, teaching biology concepts with hands-on models

MIT partners with Wabanaki Youth in Science (WaYS Program)



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Research Experience and Training Coordination Core



Prof. John Essigmann



Prof. Ariel Furst



Dr. Christa Wright



Prof. Noelle Selin

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Project 1



Bevin Engelward



Leona Samson

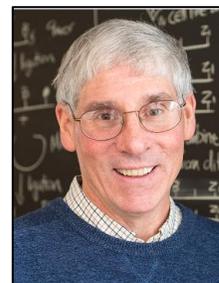


Bryan Bryson



Susan Erdman

Project 2



John Essigmann



Robert Croy



Forest White

Project 3



Tim Swager

Project 4



Desiree Plata



Ariel Furst

DMAC



Stuart Levine



Doug Lauffenburger



David Steinsaltz



Forest White

ADMIN

Dir. Bevin Engelward
Deputy Dir. Desiree Plata
Deputy Dir. John Essigmann
Tori Hile
Amanda Tat



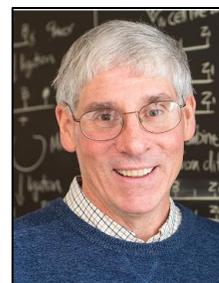
Tori Hile

CEC



Kathy Vandiver

RETCC



John Essigmann



Ariel Furst



Noelle Selin

CEC/RETCC



Christa Wright

Current Trainees & Key Collaborators



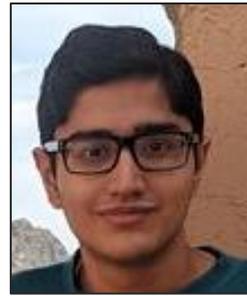
Amanda Armijo



Jessica Beard



Nicolette Bugher



Barath Baskaran



Elliot Corless



Haosheng Feng



Zhewen Guo



Anna Dormitzer



Nina Gubina



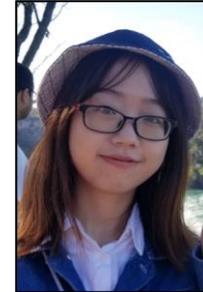
Aimee Moise



Lee Pribyl



Kristen Riedinger



Cheng Zheng



Tigist Tamir



Lindsay Volk



Vandana Singh



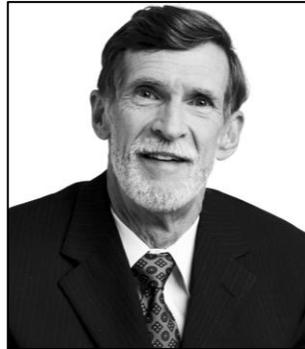
Bogdan Fedeles
Key Collaborator



Joshua Corrigan
Key Collaborator



Past Project and Core Leaders



P1: Harry Hemond



P2: Jesse Kroll



P2: Noelle Selin



RTC: Jenny Kay

Past Trainees



Disha Trivedi



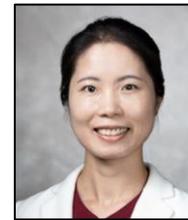
Helene Angot



Christy Chao



**Abigail
Harvey**



Maggie He



Irene Hu



Yuge Ji



**Simran
Kaushal**



Jenny Kay



Jamie Kelly



**Ishwar
Kohale**



Mingwei Li



Che-Jen Lin



Lennon Luo



Josh Moss



Dikshant Pradhan



Amy Hrdina



Lizzie Ngo



James Rowe



Tchelet Segev



Ning Thongarm



Norah Owiti

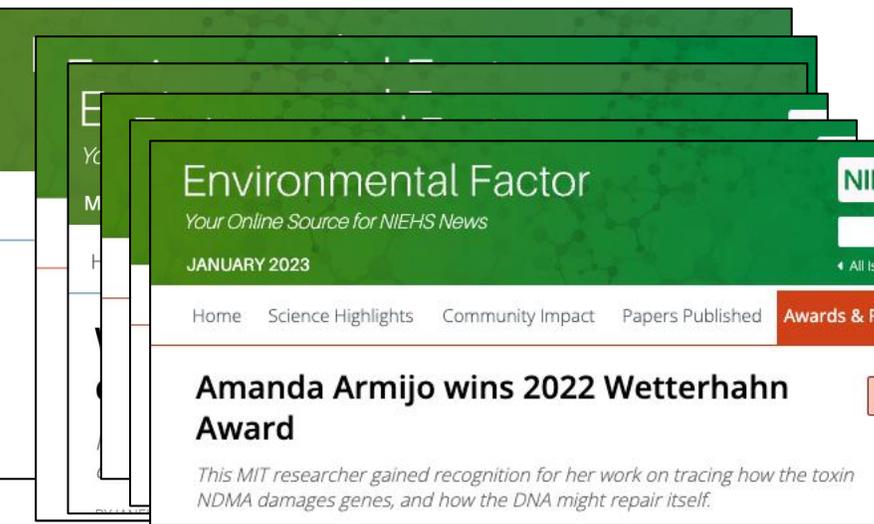


Ruqiang Lu



Marisa Chanchaoen





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Mission

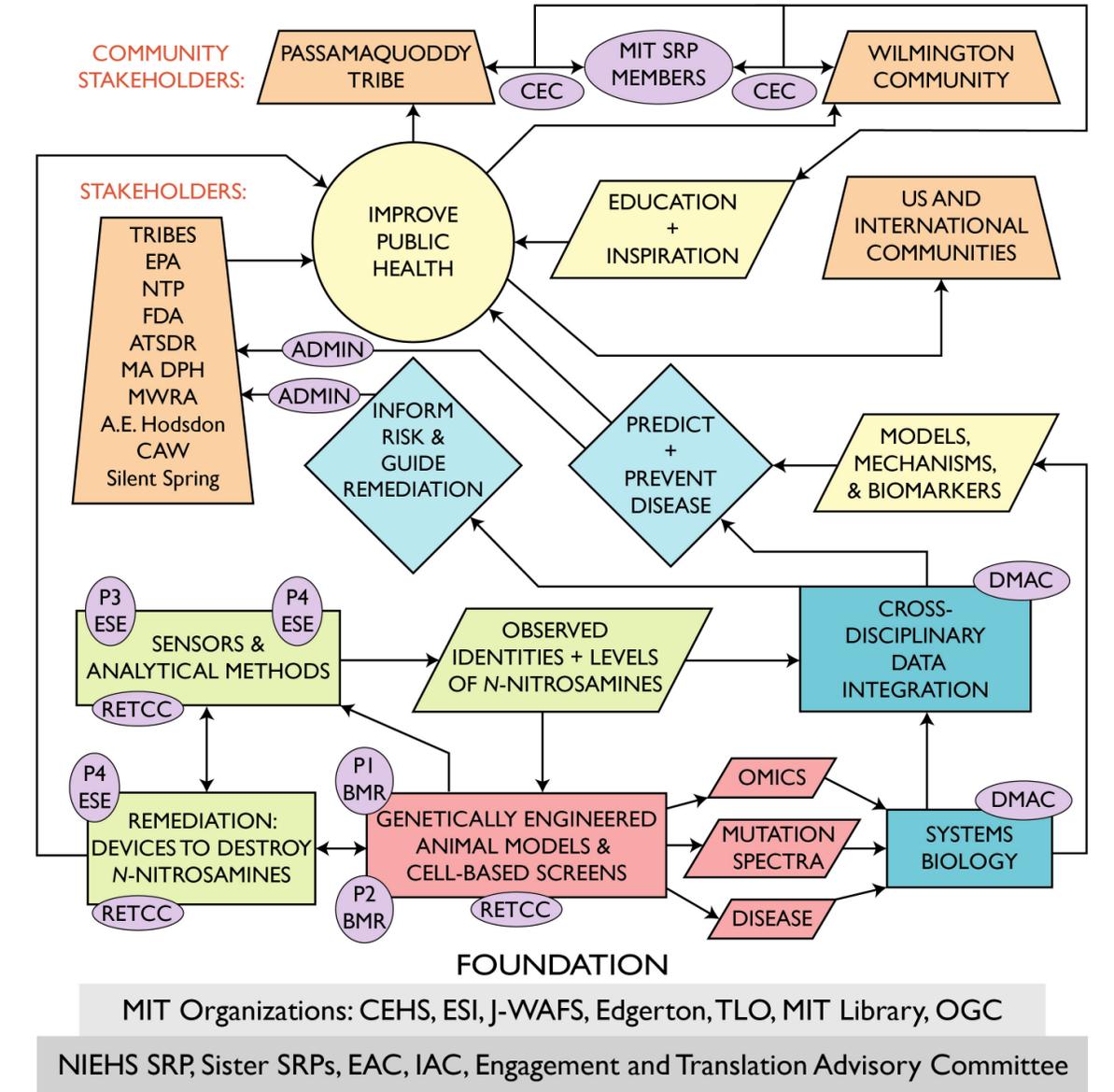
Projects

Cores

Team

Our Systems Approach

MIT Superfund Center Organizational Structure



○ Beginning/End □ Process/Activity/Assay ▱ Input/Output ◇ Decision ▭ Stakeholders ● MIT SRP