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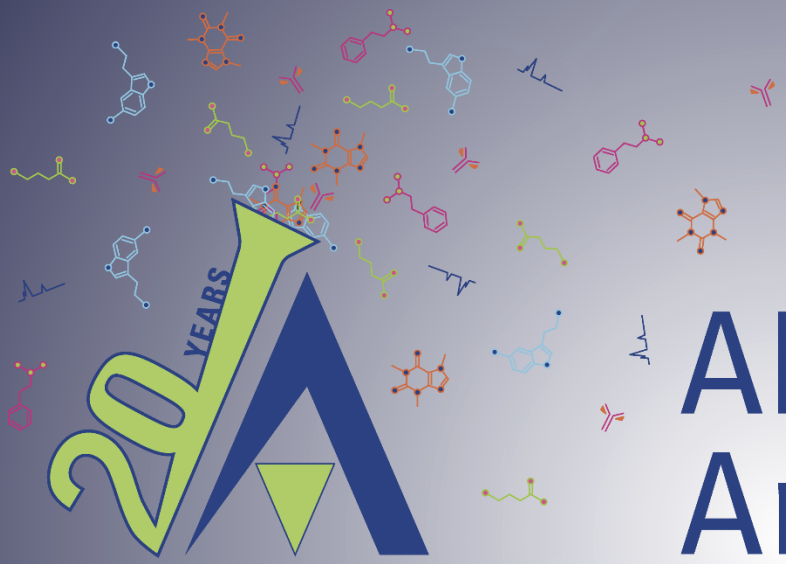

Alturas Analytics, Inc.

The LC–MS Experts

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An Application of Scientific Research in the Private Sector: Supporting Novel Drug Development on the Palouse

Jennifer Zimmer, Ph.D.
Laboratory Director, Alturas Analytics, Inc.
University of Idaho Alumna, 1995

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Exposure to **academic research** is a critical part of higher education.

What about exposure to research in the private sector?

Goals of this talk:

- Background into the process of drug development and approval in the US
- The role Alturas Analytics plays in this process here on the Palouse
- Discuss the regulatory elements governing our work to assure that pharmaceuticals approved in the US are safe and effective

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Drug Discovery: How it Happens

- New understanding of disease allows researchers to stop or reverse the effects
- In-Vitro screening of molecular compounds identifies “lead” candidates that are effective
- Existing treatments have unexpected effects on other conditions
- Novel technologies provide new ways to target specific sites in the body

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Drug Development

- **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion
- Benefits and mechanism of action
- Optimal level and delivery of dosage
- Side effects (toxicity) and drug-drug interactions

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Regulated Preclinical Research

- Ready to generate data that will be submitted to the FDA
- **Regulated Studies** prove a drug is safe before use in humans
- 2 species of animal models
- Effects of single and multiple doses
- Metabolite ID - monitor metabolites that account for >10% of systemic exposure
- Reproductive toxicity (rabbits)
- Genetic and cardiac toxicity
- Allows filing of Investigative New Drug (IND) approval by the FDA

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Clinical Development

Phase 1 Trials

- 20-100 Healthy Human Subjects
- Determine safety and dosage
- Dose escalation
- ~70% of drugs advance

Phase 2 Trials

- 100-300 Patient volunteers
- Evaluate effectiveness and side effects
- ~33% of drugs advance

Phase 3 Trials

- 1000-3000 patient volunteers
- Verify effectiveness and monitor adverse long-term use
- Compare with existing treatments
- Randomization
- ~25% of drugs advance

File for New Drug Approval (NDA) from the FDA

Phase 4 Trials

- Monitoring outcomes after market approval
- Identification of rare side effects

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Where does Alturas fit in this process?

Bioanalysis of samples collected during preclinical and clinical trials

Two major arms of our success:

1. Veteran experts in analytical chemistry
2. Experienced in compliance with the FDA

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The Technology: Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

Step1:

- HPLC- High Performance Liquid Chromatography for compound separation
- Based polarity and charge of compound
- High performance pumps, solvents, columns

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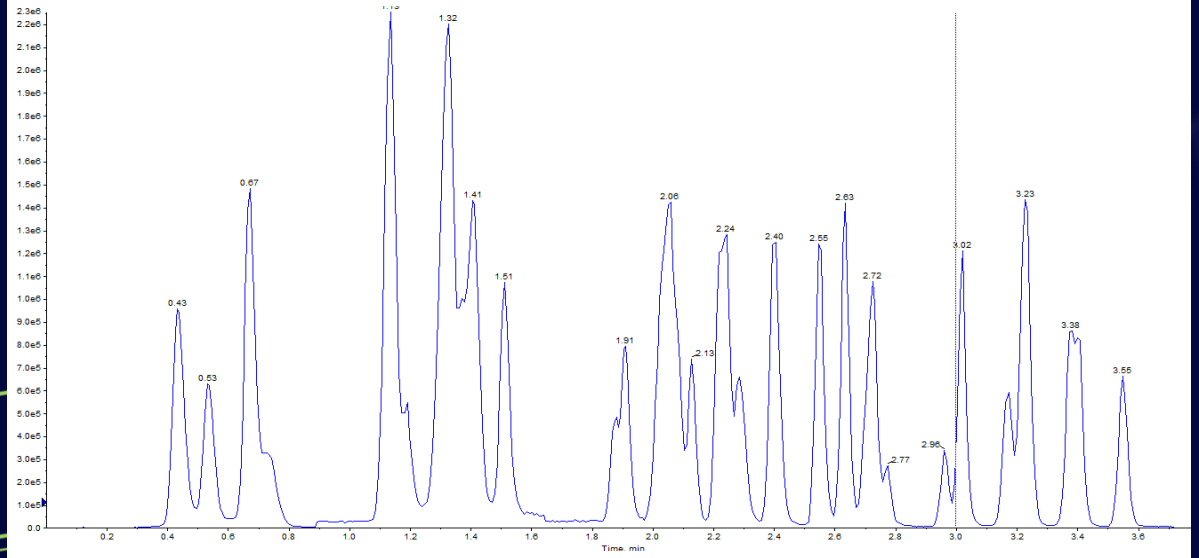
Step 1: Liquid Chromatography

The amount of time it takes an analyte to pass through the column is an identifying property

Control sample with known amounts of 40 analytes



Time (minutes)

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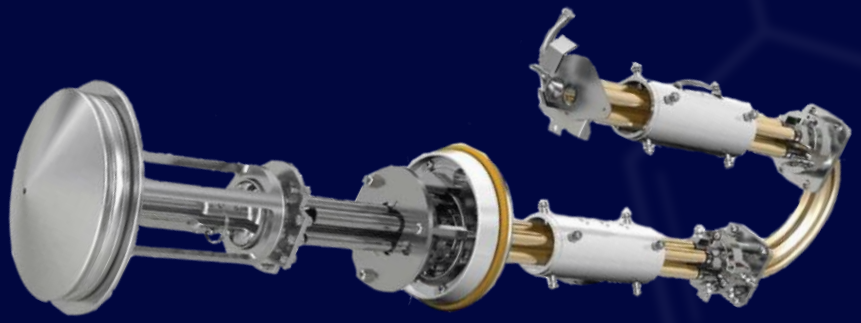
Step 2: Tandem Mass Spectrometry (MS/MS)



- Compound is converted into an ion using electrospray ionization
- Addition or loss of a proton[M+H]+ or [M-H]-
- Compound is fragmented and instrument selects a signature fragment of a specific size

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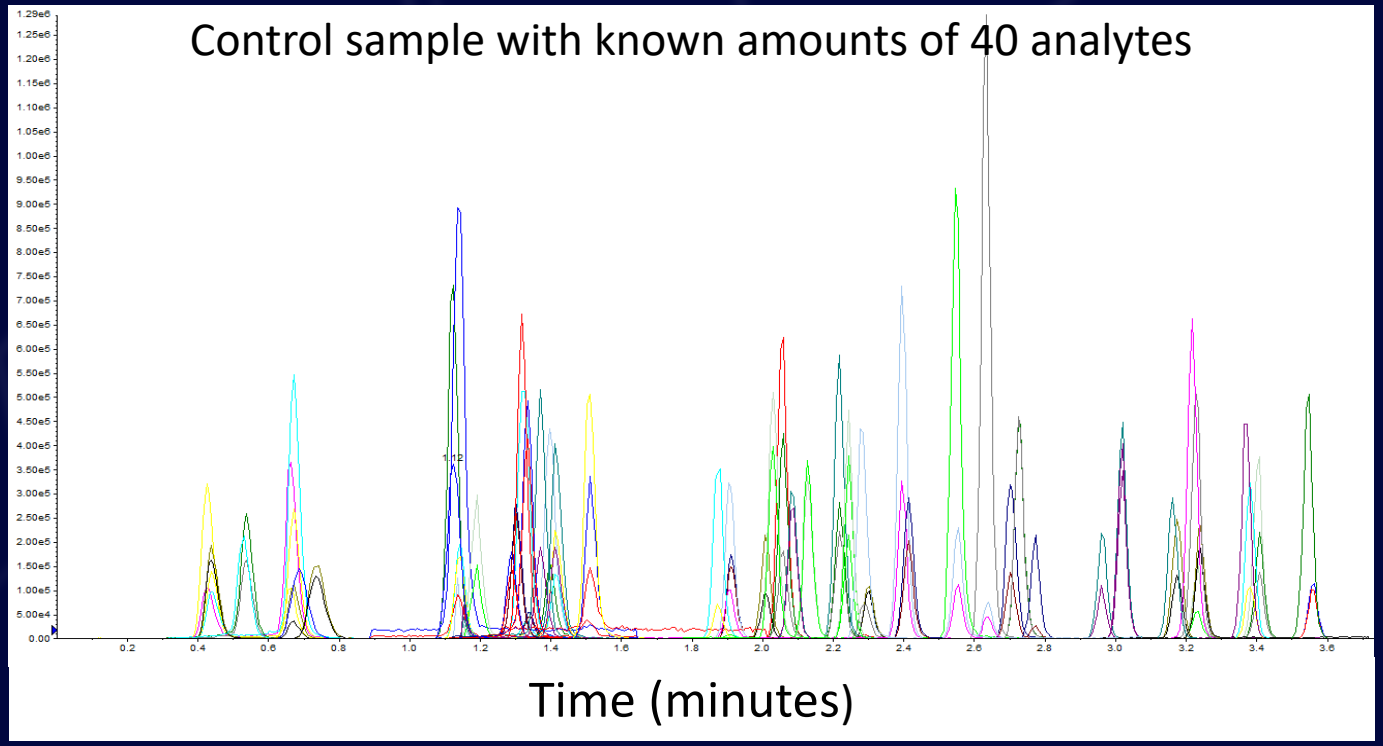
- Calculate the concentration of the drug using a standard curve generated with known concentrations of the drug
- Parts per Billion detection



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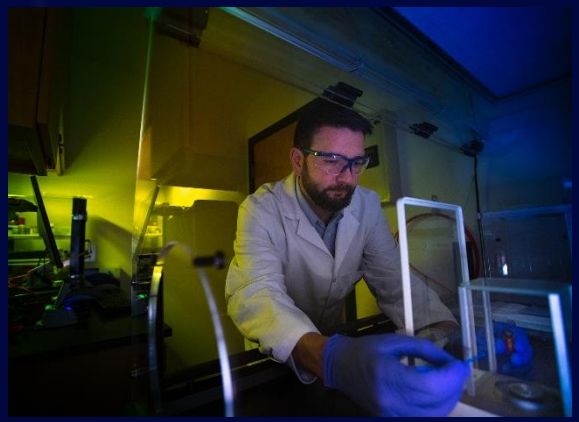
The Methods

- Clients are drug companies of all sizes looking to contract out their bioanalysis
  - From virtual companies to large pharma
- Approach Alturas to develop an analytical method to measure their compound
- All methods must be formally validated before analyzing samples
  - Is the method specific for your analyte?
  - Is the method accurate and precise
  - Tightly regulated requirements for performance



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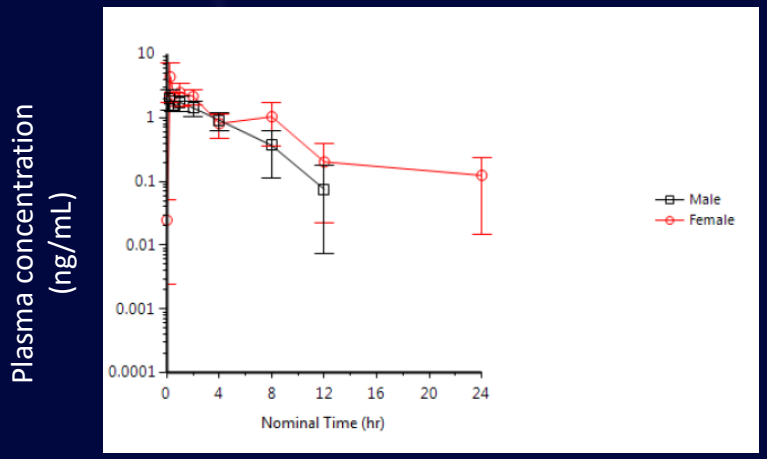
The Samples

- Thousands of samples each month are shipped to Alturas from studies taking place around the world
- Samples collected in all phases of the development process from drug discovery to Phase 4 clinical trials
- Many species and many types of matrix (plasma, urine, tissues, milk, cerebral spinal fluid and many others)
- Our work generates information used to demonstrate safety and optimal dosing



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Regulatory Elements

- To assure the integrity of work performed to support drug development the FDA institutes a set of standards:
  Good Laboratory Practices (GLPs)
- Required for **regulated preclinical studies** and sample analysis from **clinical studies**
- A quality system concerned with all aspects of study conduct from the animals to the reported data
- Ensures **standardized procedures** and allows for reconstructability of study data

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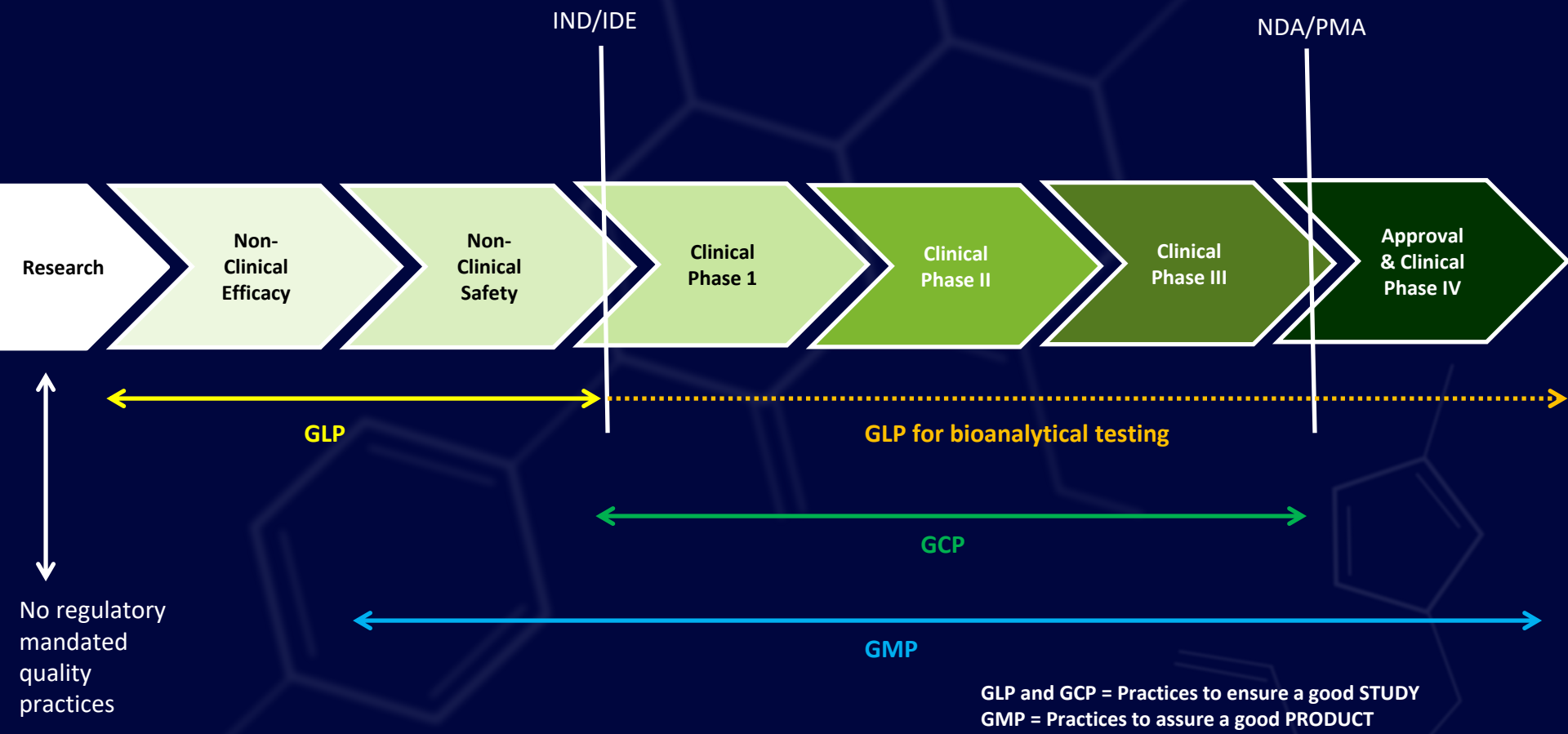
FDA Regulatory Pathway



GLP and GCP = Practices to ensure a good STUDY
GMP = Practices to assure a good PRODUCT

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Why were the GLPs enacted?

Critics Say Fraudulent-Data Trial Points to Need for Basic Reform

Who Tests the Product-Testing Labs?

Industrial Bio-Test Labs

- One of nation's oldest independent laboratories
- During its last decade (1960s-1970s), also the largest laboratory, performing more than 1500 studies
- In 1970, IBT's installed an automatic watering system, but the equipment rarely worked properly
- Faulty nozzles sprayed the room with a continuous mist, submerging the floor under a four-inch deep pool of water
- Mortality rates were so high that it was impossible to determine the toxicity of drugs being tested

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Why were the GLPs enacted?

Industrial Bio-Test Labs

- FDA pathologist started investigating
- Mortality data for rats on a long-term study showed that none of the rats had developed cancer, even at a baseline rate
- Research was found to be sloppy and fraudulent
- Rats listed as dead in one section of the study suddenly reappeared alive later in the study
- Collusion between the scientists at IBT and the sponsor to cover up unwanted test results
- Four executives successfully prosecuted
- Led to the enactment of the FDA Good Laboratory Practices (1978)

3 Ex-Officials of Major Laboratory Convicted of Falsifying Drug Tests

On the cover of the New York Times Oct 22, 1983

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Basis of the GLPS

- Documentation
  - A - attributable
  - L - legible
  - C - contemporaneous
  - O - original
  - A – accurate

- Applies to oversight of employees, facilities, equipment, maintenance schedules, reagents, materials, SOPS, reporting of results, storage and transfer of data (IT)
- Requires all work subject to oversight by an independent Quality Assurance Unit to assure compliance

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Good Clinical Practices: GCP

- Nuremburg trials post WWII led to the foundation of GCP known as the Nuremburg Code
- Early 60s there was widespread concern about the safety and control of investigational drugs
- In 1964 the World Medical Association enhanced the Nuremberg Code and created a statement of ethical principles surrounding clinical studies: **The Declaration of Helsinki**

- **“The Health of my patient will be my first consideration”**

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GCP

- Specific focus on study conduct and responsibilities of the:
  - Sponsor
  - Investigator
  - Institutional Review Board (IRB)
- Minimum requirements:
  - Subject safety (including identity)
  - Data integrity
- Unified international standards with the same purpose as stated above

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Why we do what we do: LOXO 101

- Alturas scientists have worked with LOXO-101 for 5 years
- Received FDA approval in 2018
- Effective in a variety of adult and pediatric tumors harboring gene fusions involving TRK fusions
- Targeted therapy → side effects are minimal and the effects are durable
- These therapies don't make it to market without reliable safety data

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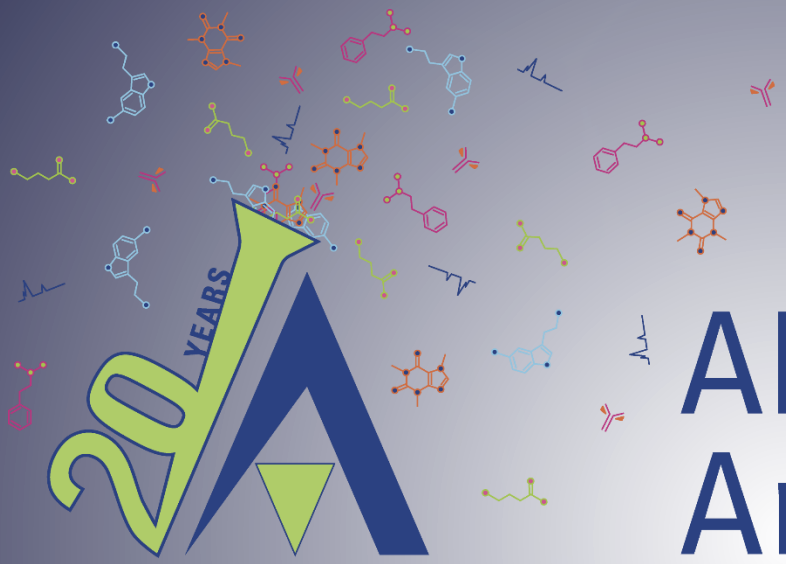

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