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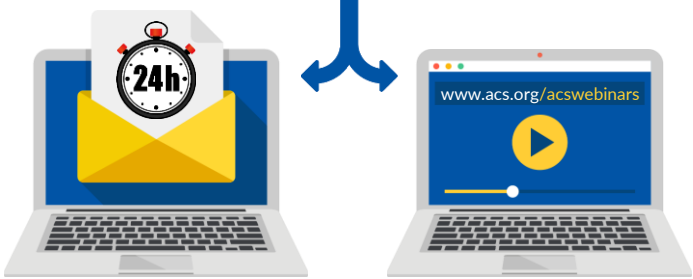

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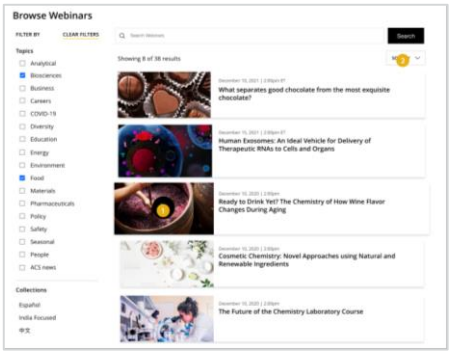

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Speaker
Principal Scientist,
Corteva Agriscience
NICOLE GOODWIN, PHD
Speaker
Director, Discovery Chemistry,
Merck
SCOTT BAGLEY, PHD
Moderator
Associate Research Fellow,
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Shared Roots with Divergent Paths

Exploring Discovery R&D in Pharma and Agrochemistry

Nikki Goodwin & Tejas Shah

5/14/2025

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Background and Introductions

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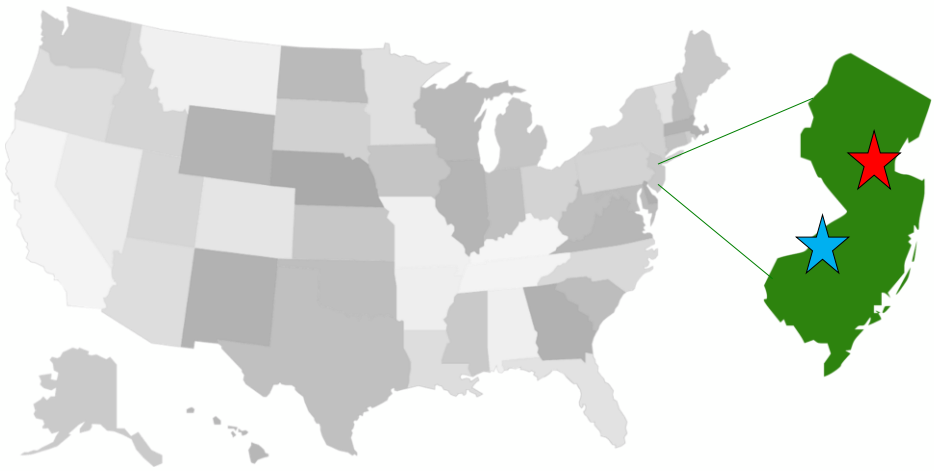
Background



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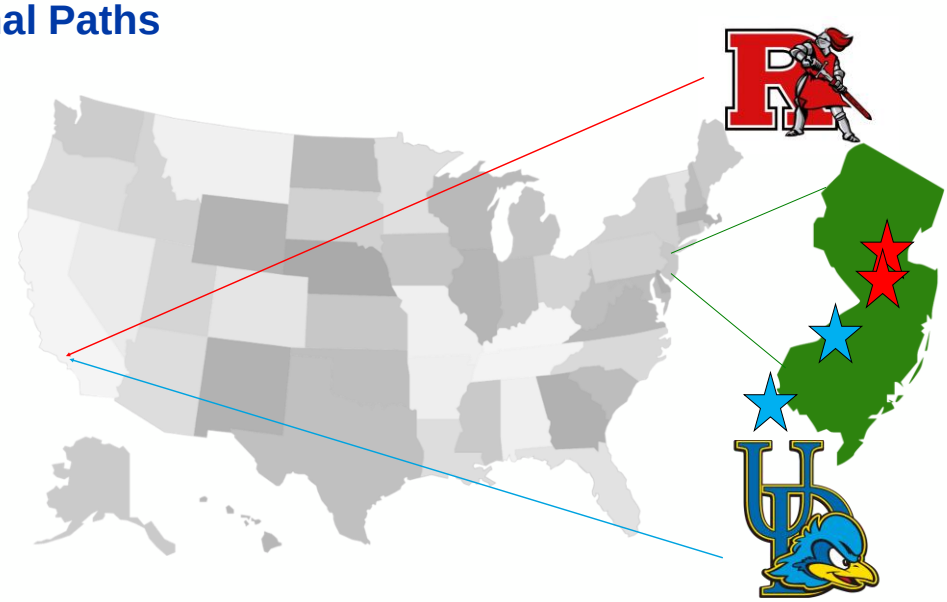
Educational Paths



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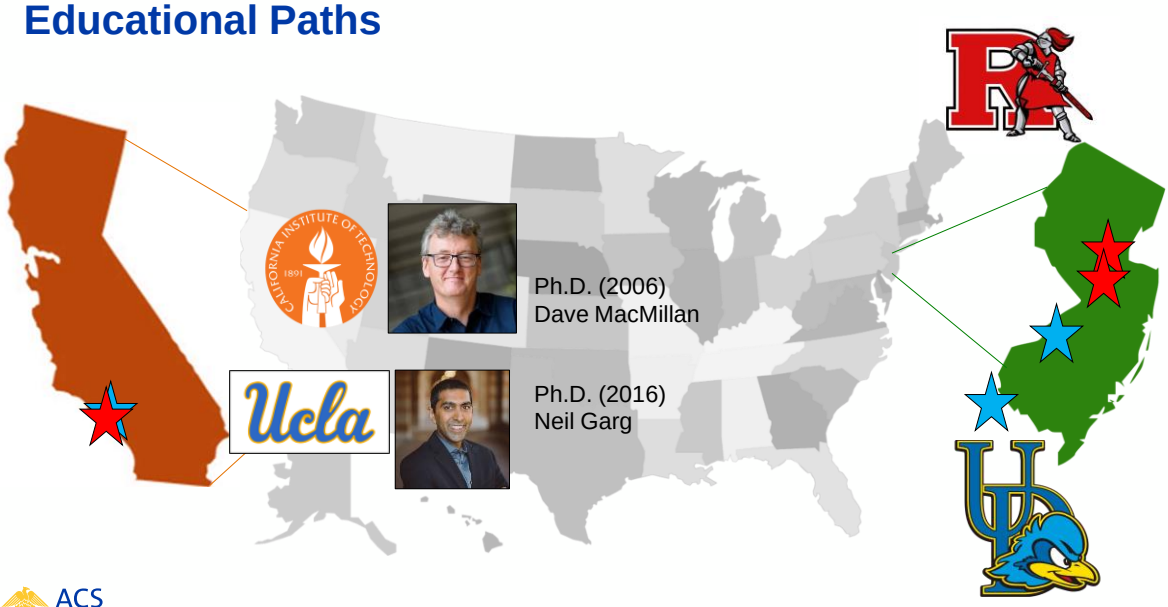
Educational Paths



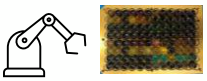
Career Path: Tejas

1. Dow Agrosciences / Corteva Agriscience (Indianapolis, IN)

   Lead Optimization Scientist
   Discovery Chemistry

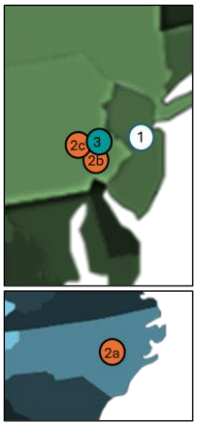
   High Throughput & Automation Leader - POWER Team
   Enabling Capabilities and Process Sciences

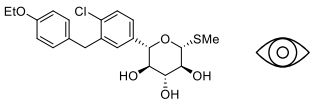
   Principal Scientist
   Integrated Discovery & Bioprocessing

Career Path: Nikki



1. Lexicon Pharmaceuticals (Princeton, NJ)
   - Medicinal Chemist



2. GlaxoSmithKline / GSK
   a. Research Triangle Park, NC
   b. Upper Merion, PA
   c. Collegeville, PA

Team Leader, Medicinal Chemist
Director, Head of Stress & Repair DPU Chemistry
Director, Discovery High-Throughput Chemistry
Oligonucleotide Chemistry Lead

3. Merck (West Point, PA)
   - Director, Discovery Chemistry

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End to End Process

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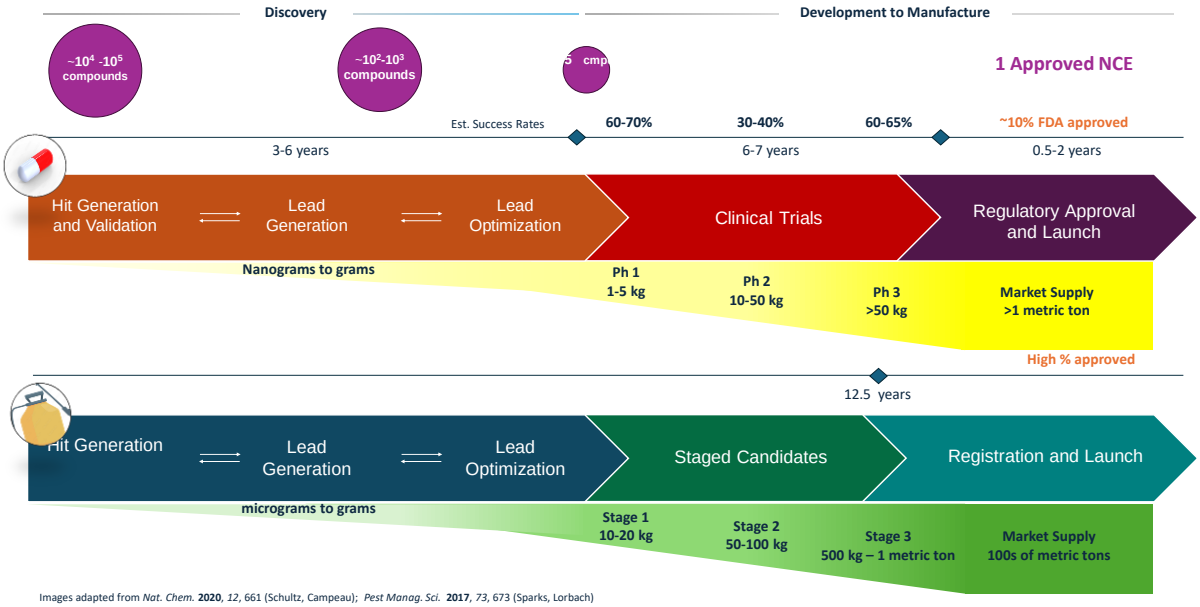
R&D Timelines



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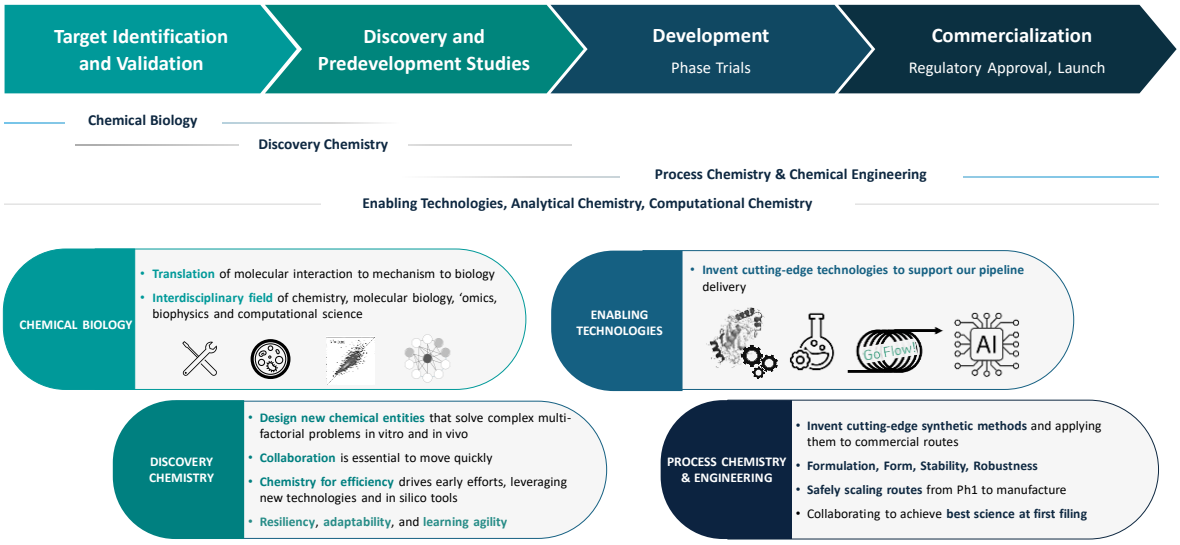
Chemistry Roles in Research & Development



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Discovery Chemistry

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Stages of Medicinal Chemistry

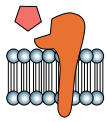
Hit Identification → Lead Discovery (Hit to Lead) → Lead Optimization → Candidate Selection → Development Clinical Trials → Regulatory Approval

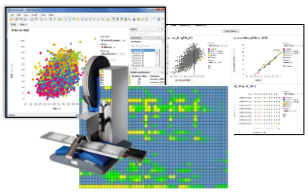
Hit Identification – Discover molecules that can interact with the drug target

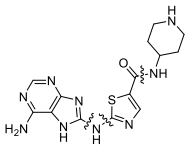
- Biochemical, biophysical, cellular, phenotypic assays among common strategies
- 1000s of hits identified and sorted

Lead Discovery – identify chemical matter that is tractable, can modulate not only pathway biology but also physicochemical and pharmacokinetic properties

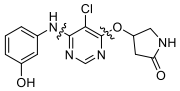
- Rapid execution of structure-activity relationships (SAR), build data sets
- Quickly make go/no-go decisions on chemical series from HTS
- Leveraging new technologies and tools in design-make-test cycle is critical



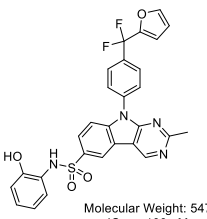




Molecular Weight: 359
IC_{50} = 600 nM



Molecular Weight: 321
IC_{50} = 1200 nM



Molecular Weight: 547
IC_{50} = 100 nM

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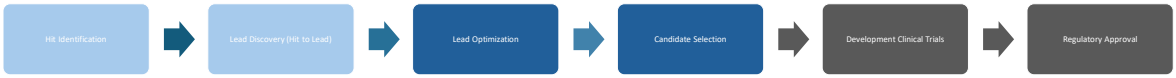
Stages of Medicinal Chemistry



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- Biochemical, biophysical, cellular, phenotypic assays among common strategies
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Lead Discovery – identify chemical matter that is tractable, can modulate not only pathway biology but also physicochemical and pharmacokinetic properties

- Rapid execution of structure-activity relationships (SAR), build data sets
- Quickly make go/no-go decisions on chemical series from HTS
- Leveraging new technologies and tools in design-make-test cycle is critical

Lead Optimization – optimize EVERYTHING!

- Potency at target
- Efficacy in translational models
- Pharmacokinetic properties: bioavailability, metabolism, excretion, tissue distribution
- Physicochemical properties: solubility, stability, form
- Safety and tolerability – on- and off-target effects in preclinical species

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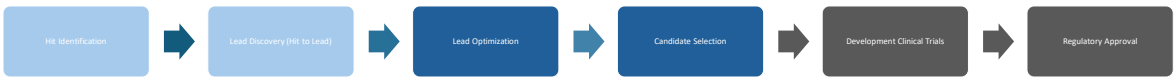
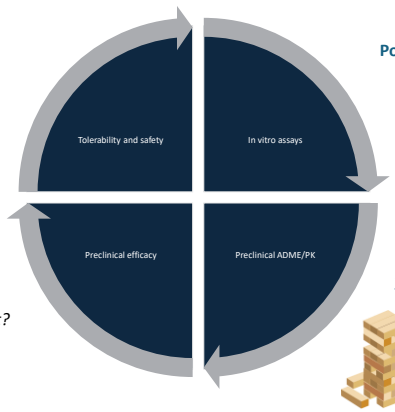
Stages of Medicinal Chemistry



Safety studies define margins

Species can be more or sensitive to some mechanisms for unknown reasons;
The most conservative margin is always used



Potency and **selectivity** in biochemical, cellular assays drives a program

Confirm species activity differences

Translational disease models are complex

What does asthma in a mouse really look like?
Can a human-specific tumor be replicated in a rodent?
Is target expression similar between species?

ADME Properties and PK
your body is designed to protect from foreigners

Metabolism pathways
Tissue distribution
Non-specific protein binding
Profile across relevant species

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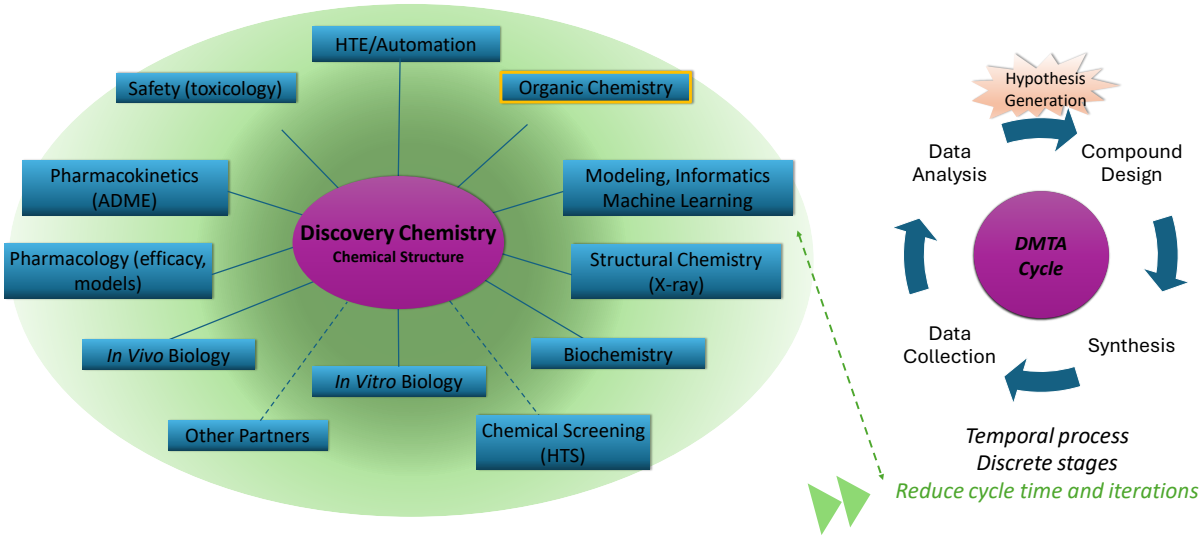
Discovery Chemistry: Central Discipline



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How Do We Screen Compounds in Agrochemistry?

Hit Identification → Lead Generation → Lead Optimization → Staged Candidates → Development → Registration

Level 1 High Throughput Screening
in-vitro and *in vivo* on-target

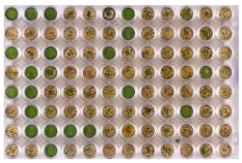
- High Volume Test
- One Concentration
- 2-5 Species per Therapeutic Area

Goal: Activity Detection? - Pass / Fail

Level 2-4: *in vivo* on more species

- Multiple Concentrations (dose response)
- Numerous Species per Therapeutic Area

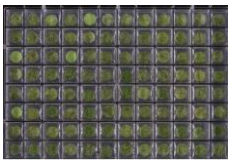
Goal: Inhibition & Confirmation Translation



Insecticide

Sap-feeding
(aphids, white fly)

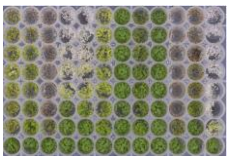
Chewing
(armyworm, moth)



Fungicide

Ascomycete
(leaf blotch)

Basidiomycete
(rust diseases)



Herbicide

Grass
(crabgrass, corn)

Broadleaf
(velvetleaf, soybean)

Additional Factors: Air Temperature, Humidity, UV Intensity, Growth Stage of Target

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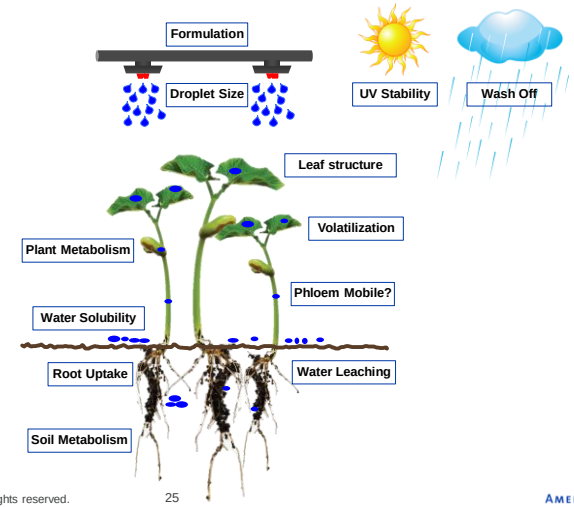
Translation Challenges

Hit Identification → Lead Generation → **Lead Optimization** → Staged Candidates → Development → Registration

- **Absorption**
- **Distribution/Translation**
- **Metabolism**
- **Degradation**

- **Organism Selectivity**

Required physical properties differ between research areas



Cost of Manufacturing with Sustainability in Mind

Hit Identification → Lead Generation → **Lead Optimization** → Staged Candidates → Development → Registration

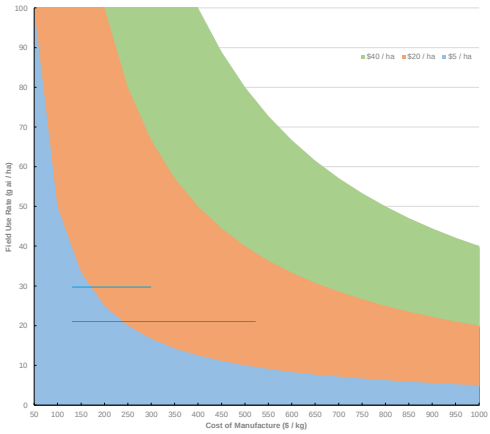
Cost per Hectare is Critical

Farmers have a budget per hectare

(Use Rate) x (COM) = $/ha

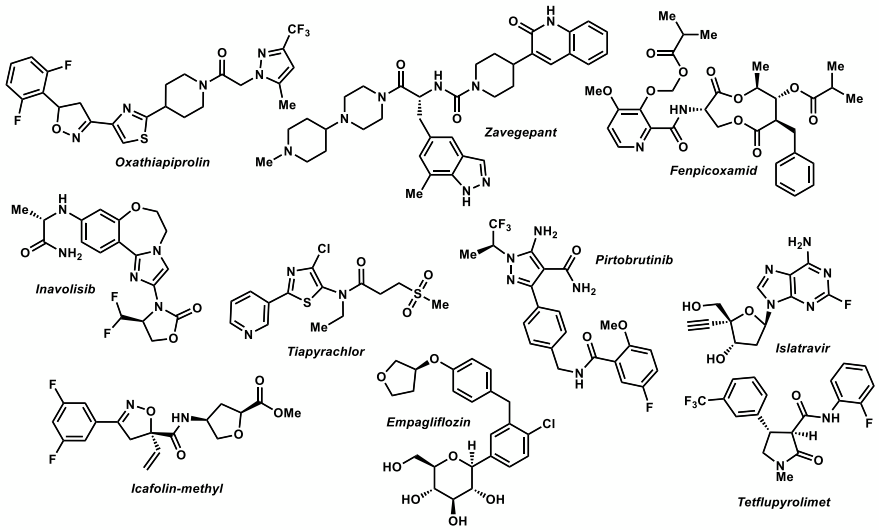
$$\frac{x\ g}{ha} \left| \frac{\$\ y}{kg} \right| \frac{1\ kg}{1000\ g} = \frac{\$}{ha}$$

Example: Manufacture using $Pd(OAc)_2$
1.0 mol% = ~7.5 g Pd per kg of product = $500 per kg
0.1 mol% = ~0.75 g Pd per kg of product = $50 per kg



1 Hectare equals = ~2 American Football fields

Can You Tell The Difference?



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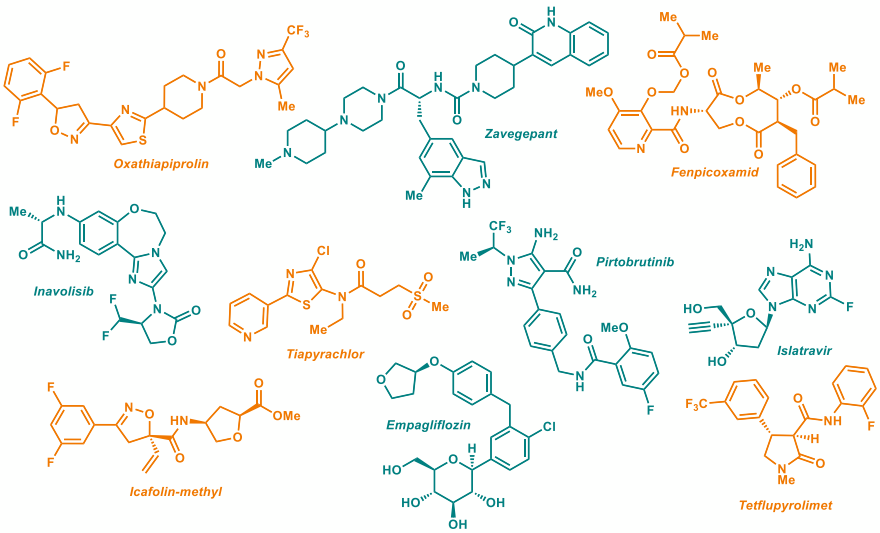
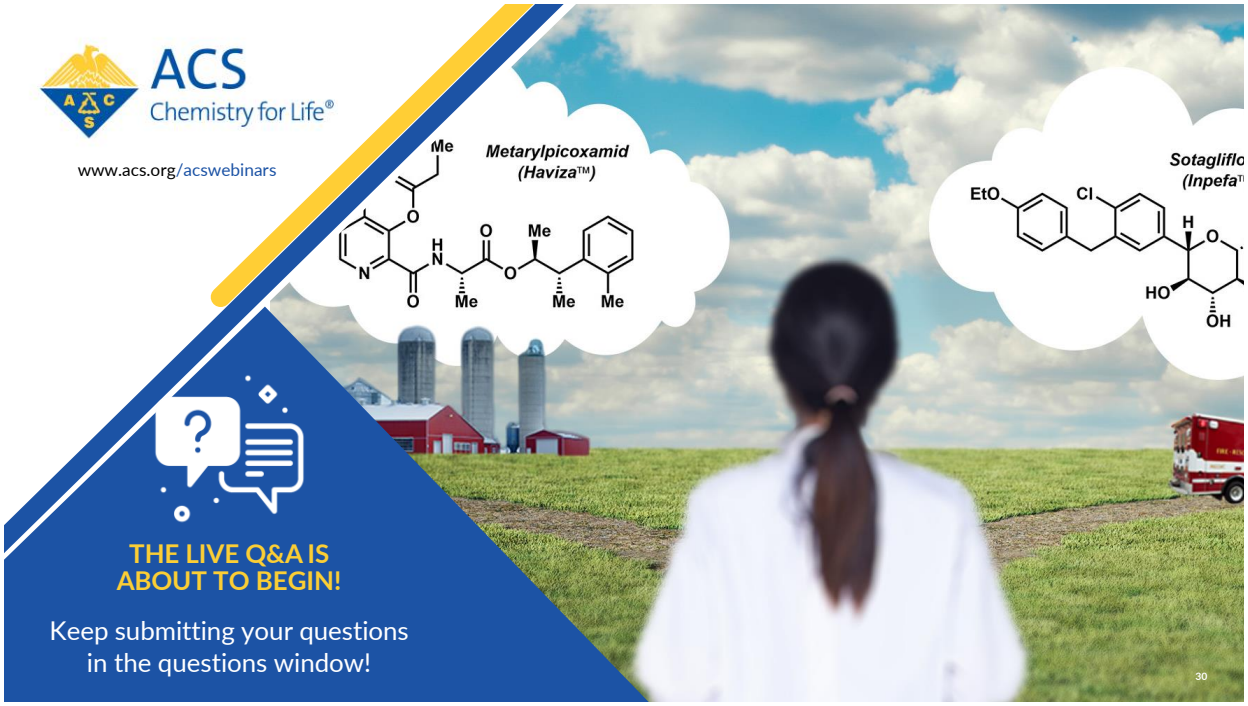


Agrochemical
Pharmaceutical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Crafting Competitive Grant Proposals
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