Type them into questions box!

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Why do we need new Crop Protection products?

- Growing more with less

![Graph showing 1 hectare fed 2 people in 1950 and 1 hectare needs to feed 5 people in 2030. Source: UNEP, Cline, Syngenta.]

- Climate change

![Map showing climate change impact with high, medium, and low levels. Source: www.plantmanagementnetwork.org.]

Why do we need new Crop Protection products?

- Resistance development and shifting pest populations

![Image of soybean field and map showing Asian Soybean Rust worldwide. Source: www.plantmanagementnetwork.org.]

- Changing regulatory landscape

![Image of regulatory environment. Source: www.plantmanagementnetwork.org.]

Classification: PUBLIC
Approximately how much was lost in billions (USD) to plant diseases and infestations from 2005 to 2015?

- 1 billion
- 3.5 billion
- 5 billion
- 7 billion
- 9.5 billion

*If your answer differs greatly from the choices above tell us in the chat!
How are crop protection products discovered and optimized

Outline

- Discovery of insecticidal spiroindolines
- Bioavailability-guided design of new aphicides
- Modern crop protection products targeting ion channels

Discovery of insecticidal spiroindolines

- Screening of a chemical library (obtained from Oxford Asymmetry, now Evotec)
- Insecticidal hit compound identified by high throughput screening
- Activity on *Drosophila melanogaster*, *Plutella xylostella* and *Heliothis virescens* at 1000 ppm
- Only compounds possessing a cinnamyl group displayed insecticidal activity

Hughes, D. J.; Worthington, P. A.; Russell, C. A.; Clarke, E. D.; Peace, J. E.; Ashton, M. R.; Coulter, T. S.; Roberts, R. S.; Molloyne, L. P.; Cederbaum, F.; Cassayre, J.; Maienfisch, P. WO2003106457
Agrochemical research: screening cascade

- *In vivo* on-target test from day 1

- Increase in tests size parallel to project stage (HTS >>> field)

Discovery of insecticidal spiroindolines: Hit-to-Lead Optimization

*Block metabolically weak positions*
- improved potency
- cumulative effect

Hughes, D. J.; Worthington, P. A.; Russell, C. A.; Clarke, E. D.; Peace, J. E.; Ashton, M. R.; Coulter, T. S.; Roberts, R. S.; Molleyres, L.-P.; Cederbaum, F.; Cassayre, J.; Maienfisch, P.; WO2003106457
Discovery of insecticidal spiroindolines: Hit-to-Lead Optimization

- Cumulative effect observed across lepidopteran target species
- Lead shows promising activity at low dose

<table>
<thead>
<tr>
<th></th>
<th>Spodoptera littoralis L1</th>
<th>Heliotris virescens L1</th>
<th>Plutella xylostella L2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC80 in ppm</td>
<td>&gt; 500</td>
<td>&gt; 500</td>
<td>&gt; 500</td>
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<tr>
<td></td>
<td>200</td>
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<td>200</td>
<td>50</td>
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<tr>
<td></td>
<td>50</td>
<td>&lt;= 12</td>
<td>&lt; 50</td>
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<tr>
<td></td>
<td>12</td>
<td>0.8</td>
<td>3</td>
</tr>
</tbody>
</table>

Primary screening [EC80-100 in ppm (mg/L)]

Properties and insecticidal activity of spiroindoline lead

Spiroindoline Lead

- Melting Point (M.p.): 168-170°C
- Aqueous solubility: 5 ppm@pH 6.5
- Log P: 5.94
- pHa: 7.88
- Photostability T50: 114 mins
- Rat acute toxicity: MLD50 > 200 mg/Kg

<table>
<thead>
<tr>
<th>Lepidopteran control (activity given as effective concentration EC80 in ppm (mg/L))</th>
<th>Spodoptera littoralis L1</th>
<th>Heliotris virescens L1</th>
<th>Plutella xylostella L2</th>
<th>Cydia pomonella L2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiroindoline 6b</td>
<td>12</td>
<td>0.8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Spinosad</td>
<td>0.8</td>
<td>0.8</td>
<td>0.2</td>
<td>12</td>
</tr>
<tr>
<td>Indoxacarb</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

Diamondback moth, Plutella xylostella, on cabbage

Check Spinosad 10 g / hl* Spirodindoline 8 g / hl*
Symptomology – insights into the mode of action

- Exploiting genetic model systems – *C. elegans* and *Drosophila*

Decades of academic work linking phenotype (visible effects) to genetic dysfunction

- Comparing chemical symptoms to genetic phenotypes identifies candidate target proteins e.g. Spiroindolines

For a recent extensive analysis of *C. elegans* behavioral phenotype:

Symptomology in *C. elegans*

- Spiroindolines induces characteristic symptoms in *C. elegans*

Genetic mutation in acetylcholine signalling discovered in 1993

Photo: Syngenta

**Hypothesis:** Spiroindolines affect cholinergic signaling

Confirming the hypothesis

- Forward genetics used to identify mutant strains resistant to SPIRO

C. elegans (Lots) + Mutagen (EMS) + SPIRO (No Growth Dose) Resistant C. elegans

Resistant mutations locate to vesicular acetylcholine transporter (VACHT)

- Binding of spiroindoline to VACHT can now be confirmed using standard biochemical approaches in vitro

Locate resistance mutations using genetic mapping and sequencing

Y48N C203Y E341K Y411N

Bioavailability-guided design of new aphicides

bioavailability-guided design of new aphicides
Which of these molecules is an or are agrochemical(s)?

(Select all that apply)

* If your answer differs greatly from the choices above tell us in the chat!
How to reach the target

Influence of physical chemical properties on the uptake into plants

The $\log P$ and $pK_a$ of agrochemicals dictate their distribution in plants

- Weak acids with intermediate lipophilicity get trapped in phloem
- Basic molecules get trapped in vacuoles
- Caveat: carrier proteins, channels can provide active transport

Which compound won’t be efficacious for aphids control?

Remember:

- Aphids are phloem and xylem feeders
- Weak acids get trapped in phloem
- Basic molecules get trapped in vacuoles (i.e. cells)

nAChR agonists for aphids control

AChBP co-crystal structure with lead

Pharmacophore:
- Cation-p interaction
- H bond donor
- H bond acceptor


Tuning physicochemical properties

- Low lipophilicity (logP < 2.5)
- Low molecular volume
- Non-basic
Modern crop protection products targeting ion channels

Audience Survey Question

How much active ingredient is used today in comparison?

- 1 kilogram
- 500 grams
- 100 grams
- 10 grams
- 1 gram

* If your answer differs greatly from the choices above tell us in the chat!
Product Safety – Who is being protected?

Product safety: studies per stage

Lead Generation
Lead Exploration
Lead Optimisation
Candidate Confirmation

Setting Direction
Mode of action alerts
Structure activity alerts
Competitor analysis

Compound design and selection
Acute toxicity
(oral/dermal/irritation)
Skin sensitization
14/28 day rat and mouse
Preliminary Pharmacokinetics (PK)
Genotoxicity screening
Dermal absorption
ADME
28 day dog
90 day rat and mouse
Preliminary development toxicity
Genotoxicity evaluation
Preliminary risk assessments

Predicting Regulatory Outcome
Acute toxicity
Genotoxicity
Carcinogenicity/Chronic 2 year study
Reproductive toxicity
Developmental toxicity
Neurotoxicity
90 day & 1 year dog
Dermal absorption
ADME – metabolites
Metabolite testing
Manufacturing intermediates
Formulation toxicity
Definitive risk assessments

In silico, in vitro

In vivo

Efficacious, safe and selective: Indoxacarb

Indoxacarb (DuPont) is an insecticide that exerts its mode of action by targeting the Voltage-gated Sodium channel

- Indoxacarb is active against Lepidoptera (moths)

Channels 2008, 2, 100.
J. Med. Chem. 2015, 58, 7093–7118
Mammalian safety of Indoxacarb

**Differential binding**

IC$_{50}$ = 1000 nM on rat Na$_V$ 1.4  
IC$_{50}$ = 25 nM on Bg Na$_V$ 1-1a  
(Bg = Blattella Germanica)

**Selective metabolism**

- In insects: Hydrolases
- In higher animals: Oxydative metabolism


Crop Protection 2000, 19, 537.

Environmental Safety – What is being protected?

- **Groundwater** – Drinking water (human exposure), irrigation water, the aquifer itself as an entity
- **Surface Water** – Drinking water, irrigation water, aquatic organisms (fish and aquatic plants)
- **Soil** – Persistence in soil, topsoil erosion, carry-over into follow on crops
- **Non target insects, plants and the organisms**
  - Bees, beneficial insects, worms, off target plant species, birds, field dwelling mammals
- **Air** – long range transport, atmospheric degradation, vapour movement

Volatilization  
Spray drift  
Runoff  
Leaching
Efficacious, safe and selective: Anthranilic amides

Anthranilic amides bind to the insect ryanodine receptor in muscle cells

**Intrinsic target-based selectivity:**
**Insect vs. Mammal**

<table>
<thead>
<tr>
<th>EC50 (nM)</th>
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<tbody>
<tr>
<td>Cockroach</td>
</tr>
<tr>
<td>Fruit Fly</td>
</tr>
<tr>
<td>Mouse</td>
</tr>
<tr>
<td>Rat</td>
</tr>
</tbody>
</table>

Active in the field at rates as low as 5 g/ha!
(typical rate for organophosphates = 1 Kg/ha)

Crop: Cauliflower
Source: Taiwan, Syngenta trials 2007

---

Modulation of soil persistence

Chlorantraniliprole (DuPont)

- M.p. (°C) 208-210
- logP 2.76
- pKa (acid) 10.8
- Water solubility (mg/l, 20-25 °C) 1.0
- Water DT50 10 d (pH 9, 25 °C)
- Soil DT50 < 2–12 mo

Cyantraniliprole (DuPont/Syngenta)

- M.p. (°C) 224
- logP 1.94
- pKa (acid) 8.8
- Water solubility (mg/l, 20-25 °C) 14.24
- Water DT50 < 1 d (pH 9, 25 °C)
- Soil DT50 average 32 d

Improved plant mobility
Increased spectrum of insect control (aphids and leafhoppers)

(Data from BCPC Pesticide Manual)
CP Research & Development

Discover 100,000 compounds

Evaluate 30 compounds

Profile 5000 compounds

Launch 1

$280m

8-10 years

Uncertainty

Multifunctional teams

Acknowledgements

Chemistry
Jérôme Cassayre
André Jeanguenat
Otmar Hueter
Chris Godfrey
Paul Worthington
Peter Maienfisch
Louis-Pierre Molleyres
Thomas Pitterna
Fredrik Cederbaum
Rick Roberts
Andreas Beck
Laura Wildsmith

Insect Biology
Patrik Hoegger
Anke Buchholz
Elke Hillesheim

Biokinetics
Myriam Daniels and team
Rob Lind

Electrophysiology
Jim Goodchild
Francesca Cash*
Prof. Richard Baines*

Biochemistry
Fergus Earley
Liz Hirst
Penny Cutler
Janet Phillips

Genetics
Ann Sluder**
Sheetal Shah
Ralph Clover**
Min Shi

Product Safety
Steve Hadfield
Caroline Winn
Mark Slater
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C. elegans biology
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and team

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Thinking Outside the Pillbox: Lead Generation and Optimization in Crop Protection Research

Tejas Shah
Research Investigator, Corteva Agriscience

Fides Benfatti
Team Leader, Research Chemistry, Syngenta Crop Protection.

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