Biopesticides – The most common mistakes you want to avoid

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Not for dummies ...

Societal challanges
Mechanism of action
Biofungicide
Registration
Efficacy
Patent
Mechanism of action
Registration
Disease
Registration
Societal challanges
Crop protection
Efficacy
Fermentation
Market
Ecotoxicology
Toxicology
Agriculture
Strategy
Formulation
Active ingredient
Microorganism
Regulation
Efficacy
Agriculture
Market
Efficacy
Crop protection
Formulation
Industry
Microorganism
Registration
Regulation
Crop protection
Formulation
Green
Societal challanges
Mechanism of action
Patent
Residues
Biopesticides
Safety
Market
Microorganism
Patent
Bioproduct
Crop protection
Formulation
Regulation
Agriculture

Many of them depart, a few arrive…

Many of them depart, a few arrive…

- Less than 0.1 % of the potentially bioactive microbial biocontrol agents reaches the market (estimation based on scientific journals, ‘grey literature’, theses)
- Increased research efforts in the last 10 years (especially in India, China, Africa, Central and South America)
- Mainly ‘old’ active ingredients on the market (identified 30 years ago or more)
- Most are new strains of the same well-known species
- When arrive, quite often less effective than chemical standard

Do we know all the reasons?

Economic limiting factors

- **Registration: Costs for registration are often prohibitive (about 1.2-1.5 M€ in Europe, 1 M$ in USA)**
- **Narrow market: microbial PPPs often highly specific and limited to organic and mPPPs manufacturing companies used to be small and numerous (90% of the chemical market in 7 companies)**

Consequence: cost of mPPPs vs. chemicals is higher and RoI is lower – IS IT STILL TRUE?

HP: Effective mPPP integrated with conventional pesticides to reduce residues on food and for soil applications

New chemicals = specific, 1-2 treatments/year to prevent resistance

Do we know all the reasons?

Limiting factors in the use

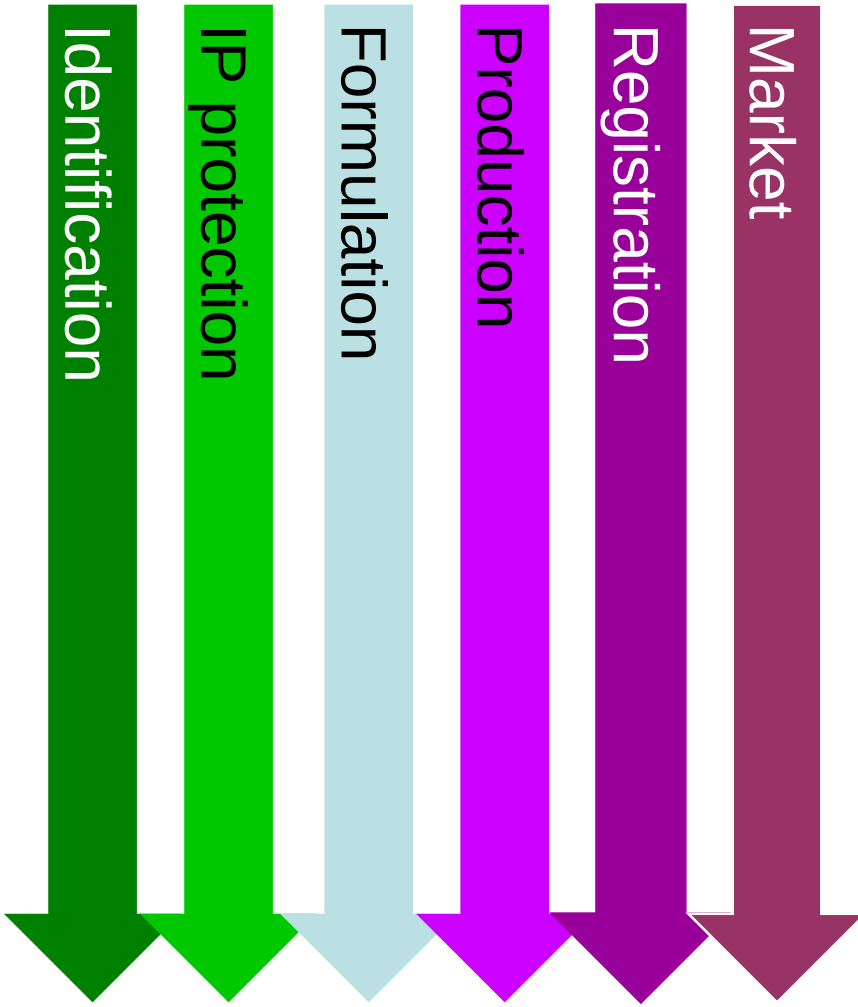
- **Efficacy: less effective and inconsistent (higher risk of losses and dependence on environmental conditions)**
- **Knowledge: high technical skills for a successful use; need confirmation in each new environment**
- **Cost for growers: expensive, complicate, need monitoring**

Consequence: mPPPs vs. chemicals are weak and difficult – IS IT REALLY TRUE?

HP: Effective mPPP integrated with conventional pesticides: when there is an advantage vs. chemical and conditions of application are correct

Development process

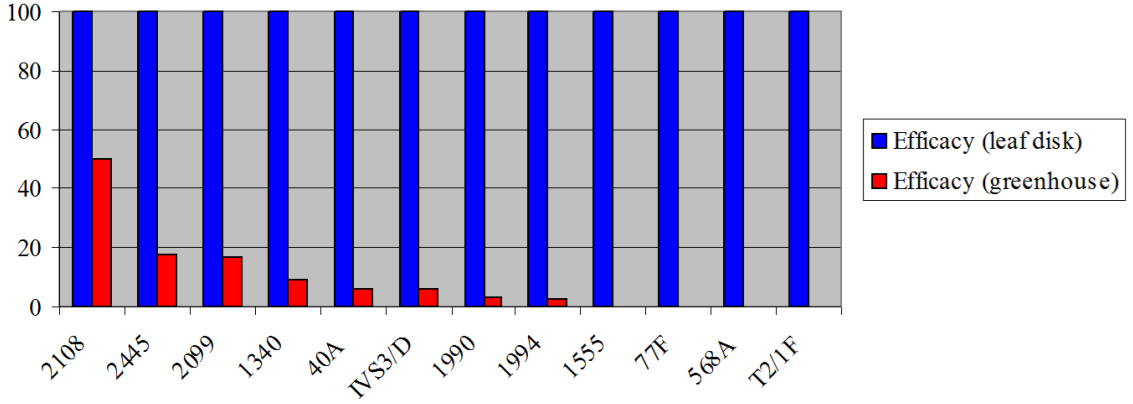
- **Identification**
  - At strain level
  - Effective (pathogens)
- **IP protection**
  - Patent
  - Confidentiality
- **Formulation**
  - Shelf life
  - Increase field efficacy
- **Production**
  - Industrial scale-up
  - Reducing cost of production
- **Registration**
  - Tox and Ecotox
  - Efficacy
- **Market**
  - Integration in IPM
  - Label extension

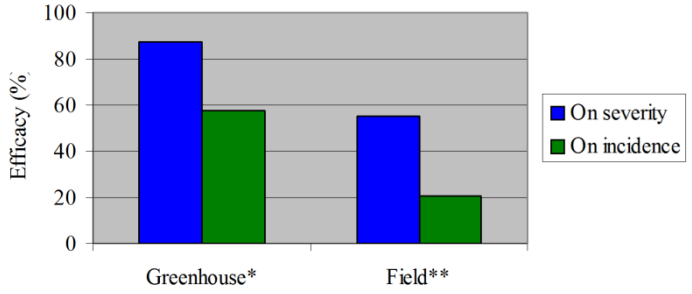


Isolation

Dual culture or leaf disk screening

- **Advantage: high throughput screening**
- **Bias: Selection of microorganisms producing active metabolites (antibiosis) under the conditions used in the trial (substrate, temperature, RH, etc.)**
- **Real conditions of use are far from the lab conditions (i.e. conidia need to germinate before being active)**

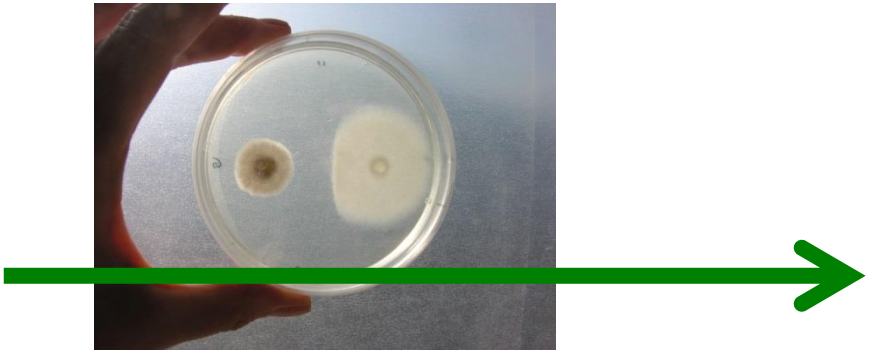




Isolation - Recommendation

In planta screening – conditions closed to reality

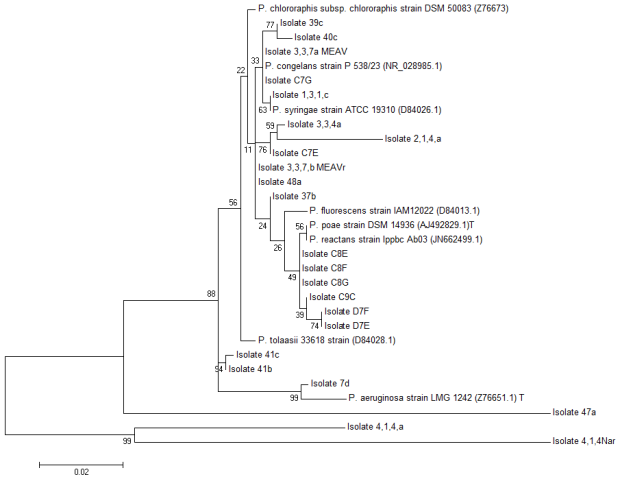
- Small scale trials on plantlets: good compromise
- Lower number of potential candidates screened
- More robust and trustable results
- Dual culture or leaf disk test only for specific objectives: i.e. to characterize the direct effect against the pathogen, preliminary trials to check the role of metabolites against the pathogen



Identification

Correct identification at species level

- Often identification comes after several efficacy trials: with bad surprises…
  - Species related to human pathogens, production of metabolites of concern, plant pathogen, etc.



Identification - Recommendation

Correct identification at species level

- Identification as early as possible!
- Clear taxonomy – molecular level
- If isolated from environment, cross-check with strains of the same species used and biopesticides
- Specific markers for strain identification (later stage, although compulsory for registration)
- Accurate check of the existing literature at species level

Identification – Recommendation

Other useful tips:

- Prefer strains, which does not grow @ > 36°C
- Verify feasibility of a large scale fermentation (cost of substrate, submerged vs. solid state, fermentation yield, time, etc.)
- Check environmental stress tolerance (minimal medium, water, high/low temperature, freezing, desiccation, water activity, UV, etc.)
- Test control efficacy of washed cells vs. culture broth or culture broth + cells

IP protection

Publishing is ‘very urgent’! Evaluation of scientists is based on publications

- Investing research money in isolating new microbial strains is less ‘convenient’ for the career
- New strains are offered to industries without IP protection
- Patents are filed in very early stage, new strains still need years for industrial development, IP protection is limited to few years (patent expire)
- Patents for strains of ‘known’ species a more difficult (claims should be narrow or specific thus limiting formulation options and market)

IP protection - Recommendation

Patent as late as possible (without disclosing any result before)

- Do not publish any preliminary result at conferences, abstracts, in posters; strain in restricted culture collection (Budapest treaty)
- New strains are patentable only if show an advantage to the state of art (include existing strains in you trials)
- Patenting microorganism + formulation may restrict your freedom later

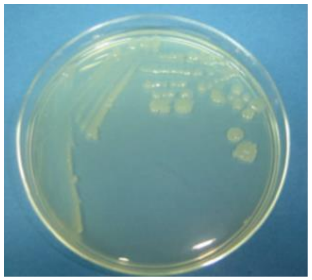
Patent vs. confidentiality

- Carefully check with patent attorney: i.e. confidentiality is preferable for fermentation process, formulation

Formulation

Formulation may play an important role (survival, efficacy, metabolites, shelf-life)

- Good microbial active ingredient may be discarded because tested without formulation
- New strains are often offered without formulation to industries (efficacy trials with washed cells or cells in culture broth)
- Changing formulation at a later stage may influence efficacy
- Formulation is often strictly related to the fermentation process



Formulation - Recommendation

Formulation should be finalized as early as possible

- Define the type of application of the MOs (i.e. soil, leaf, post-harvest): optimal formulation may vary among uses
- Do not patent formulation if possible or prefer wide claims of formulation
- Check the shelf-life of formulated product as early as possible
- Carry out efficacy trials with the final formulation

Registration

Registration is often the last step prior entering the market

- Registration of some promising candidates may be complex and expensive (abandoned in a later stage because not economically sustainable)
- Registration at strain level, however can be easier to register a strain belonging to a well-known species
- Registration of poorly characterized species can be difficult
- Mechanism of action may impact on registration (i.e. antibiotic producer may be more difficult to register

Registration - Recommendation

Registrability should be checked as early as possible

- Accurate literature review of closely related species
- Strains of well-known species vs. Strains poorly characterized: pros and cons
- Check for presence of metabolites of concern as early as possible
- Strains belonging to poorly characterized species: produce scientific evidences (as many as possible) on fate in the environment, mechanism of action, impact on air, soil, water MOs (good items for publication)

Market

Market needs are not being met (quite often)

- Not always a big market (pathogen/crop) can be satisfied (i.e. pathogens with a fast epidemic growth are not suitable for biocontrol, high risk aversion, low market tolerance for symptoms, etc.)
- Unsuitable mechanism of action against the pathogen (low or inconsistent efficacy)
- Dual culture test can drive to big disappointment in field trials (it is a suggestion not a recommendation)
- Most of the registered strains have been tested against the most important pathogens (‘no publication’ does not mean ‘no test’, most frequently means ‘negative result’)

Market - Recommendation

When looking for a market (pathogen/crop)

- Define the way of application, the most suitable mechanism of action, identify frequent environmental conditions on the crops: screening for new strains should start form here
- Be wise, but courageous: we need new species on the picture
- Prefer mechanisms as reduction of inoculum; diseases with high market tolerance to symptoms; uses as reduction of pesticides residues
- Avoid diseases where even chemicals often fail (with few exception)
- Talk with experts (researchers, advisors)

Define your roadmap and follow it

The game of Goose (giuoco dell'oca) was Invented by Francesco de Medici in XVI century

Define a roadmap and follow it

The game of Goose (giuoco dell'oca)

Roll the dice and move your counter one square for each spot on the dice

- **If your counter lands on a Goose square you can move again the number of spots of your original throw (waive a test)**
- **If you land on the Inn, miss a turn (additional data are requested)**
- **If you land on the Prison, miss three turns (more additional are requested)**
- **If you land on Dead, go back to square 1 and start all over again! (did you choose the wrong strain?)**

Thank you for your attention !!!

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