SCIENCE MEETS LIFE

VIB – R&D

Crop Innovation & Business Meeting

April 3rd 2017

Els Beirnaert, Senior Manager New Ventures

VIB's mission

Conduct frontline life sciences research
"Excellence in Science and Innovation"

Translate results into benefits for society
"Excellence in Tech Transfer and Entrepreneurship"

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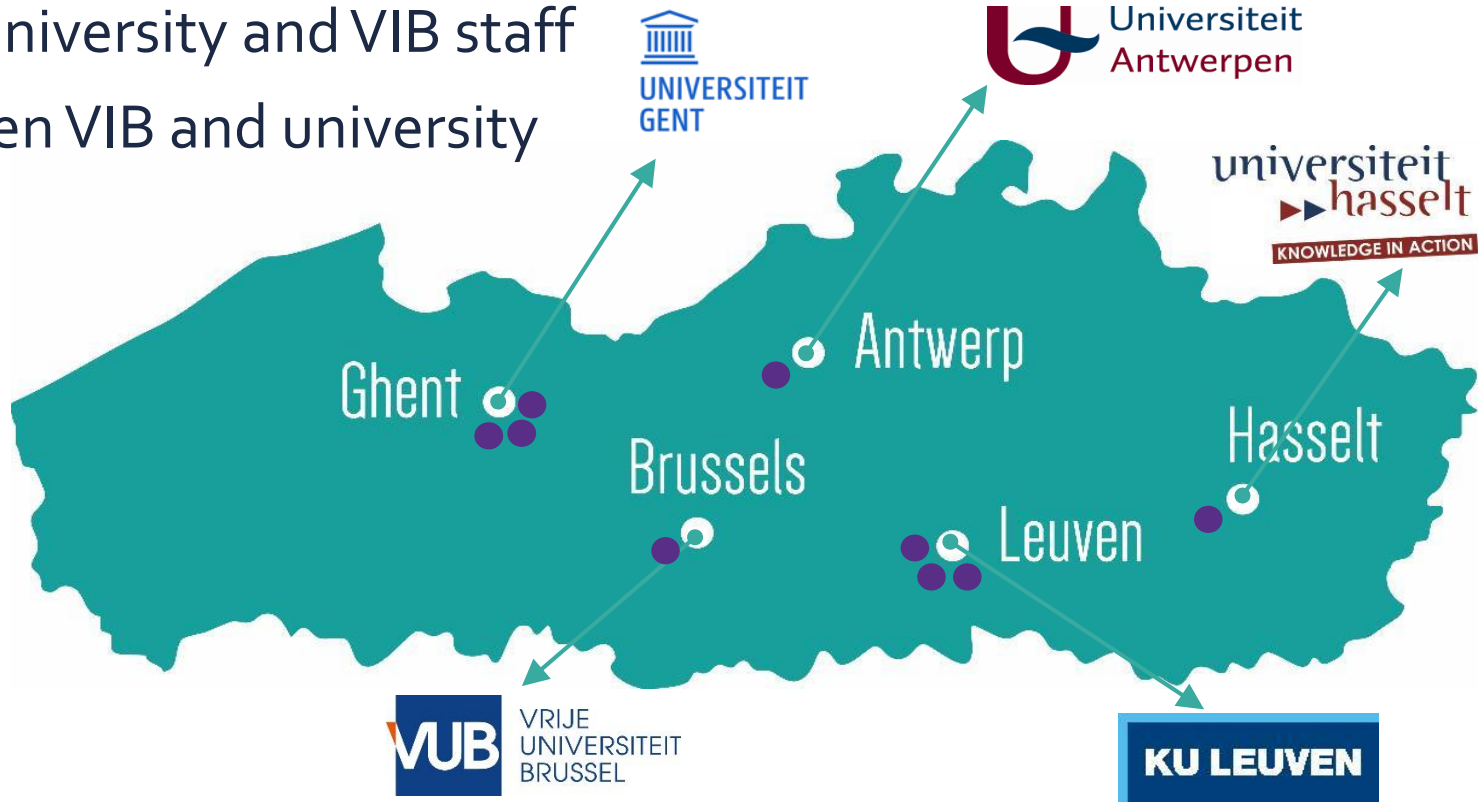
VIB's road to success

- University campus
- Complementary expertise of university and VIB staff
- Framework agreement between VIB and university
- Mutual added value
- Share return on investment
  - Publications: 2 affiliations
  - IPR: joint IP (VIB in charge)
- VIB research budget: 120 M€



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High-quality, focused research areas

Plant Systems Biology

Cancer Biology

Neurobiology

Translational Neuroscience

Inflammation

Medical Biotechnology

Structural Biology

Microbiology

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Strong track record for innovation in Agro

- UGent: cradle of plant biotechnology
- 1982: Foundation of Plant Gentic Systems (PGS)
- VIB's Leading research center ('PSB') in plant science
- Foundation of 3 agbio spin-off companies:
  - **deVGen (1997)**
    - RNAi
    - Hybrid rice (acquired by Syngenta in 2012)
  - **CropDesign (1998)**
    - Yield traits
    - Rice & corn
    - HTP phenotyping (acquired by BASF in 2006)
  - **Agrosavfe (2013)**
    - Innovative formulations for crop protection
  - **2 start-up projects incubating**

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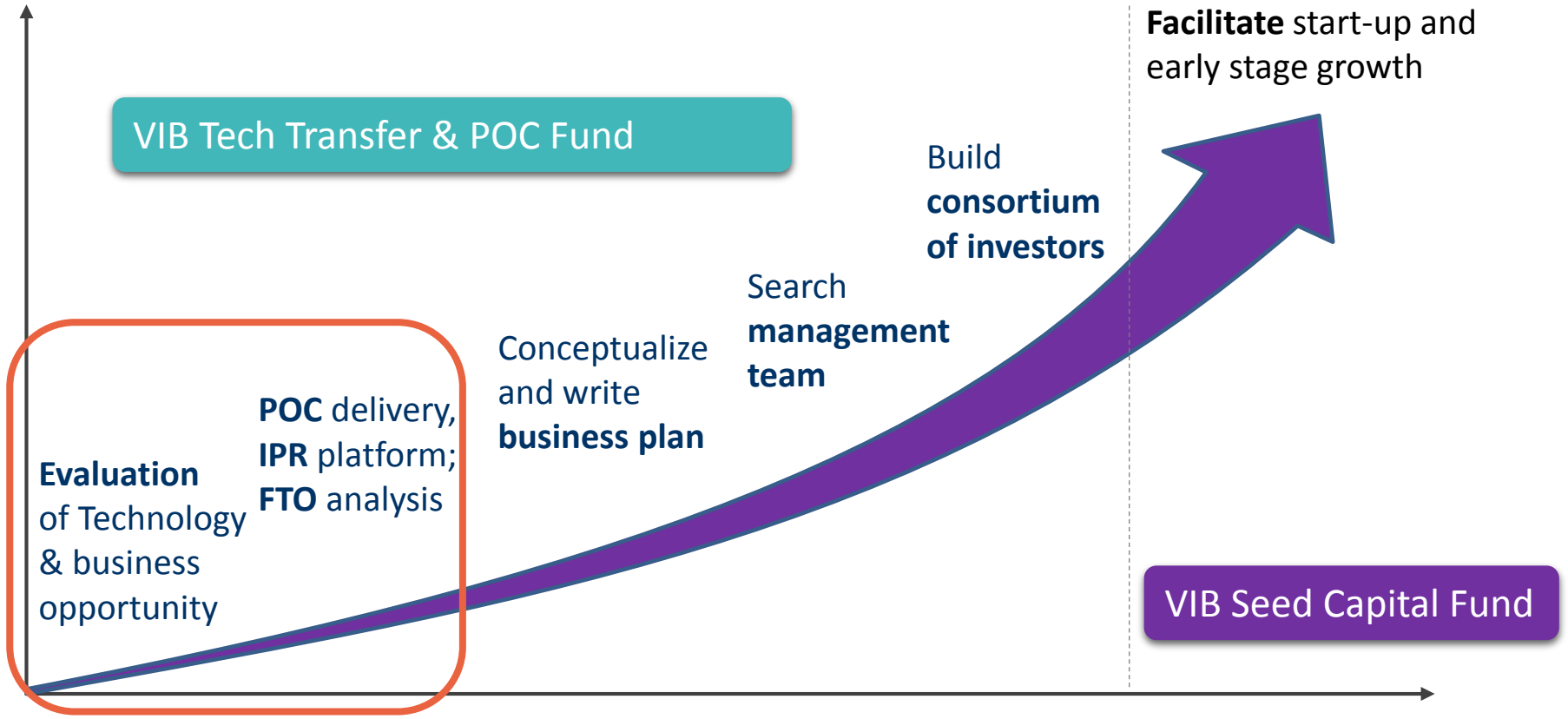
VIB approach towards start-ups



Shift towards longer incubation time:
Derisking science – Need for stronger POC
Derisking business – Start-up management team

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The Power of Aggregation

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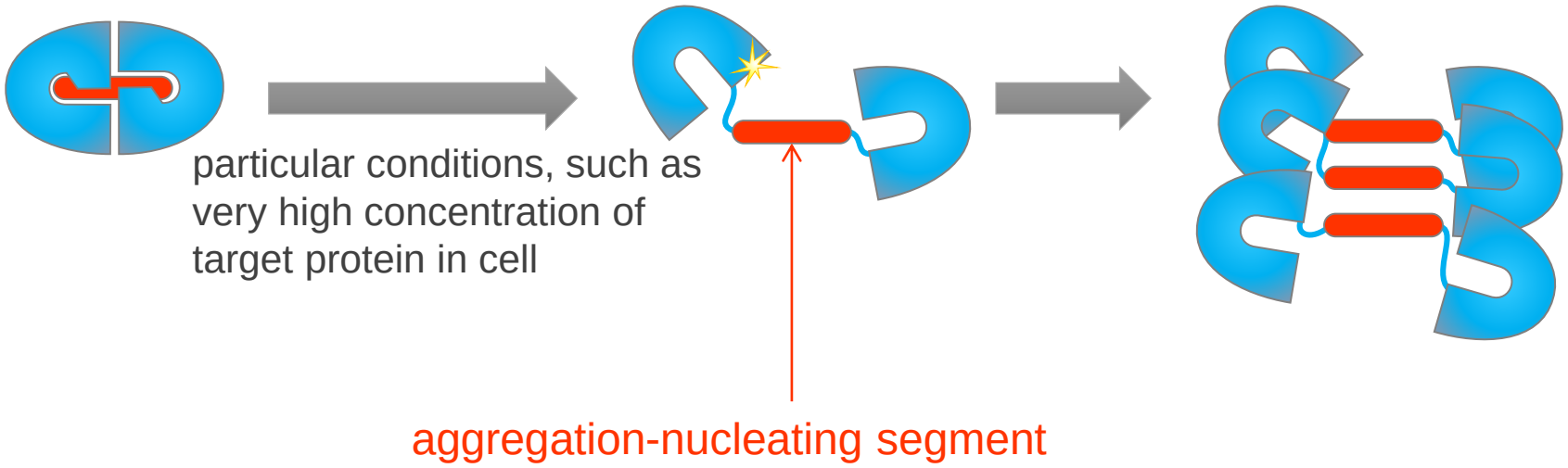
Executive summary

- Novel proprietary technology for targeted knock-down of proteins through protein-protein aggregation
- Broad and differentiating technology platform with multiple ag-applications:
  - **Crop protection**: targeting proteins from organisms causing damage to plants (pests and diseases)
  - **Crop improvement**: targeting proteins from the plant
- Two ways to deploy the technology:
  - As transgenes for GM crops: crop protection / improvement
  - As peptides for crop protection
- IP protected by broad patent families owned by VIB

Protein aggregation process in nature



Protein aggregation

- is specific : proteins preferentially associate with themselves when aggregating
- is not determined by the entire protein sequence but by short sequence stretches which can be identified by computer algorithm
- can result in functional knock-down of protein function

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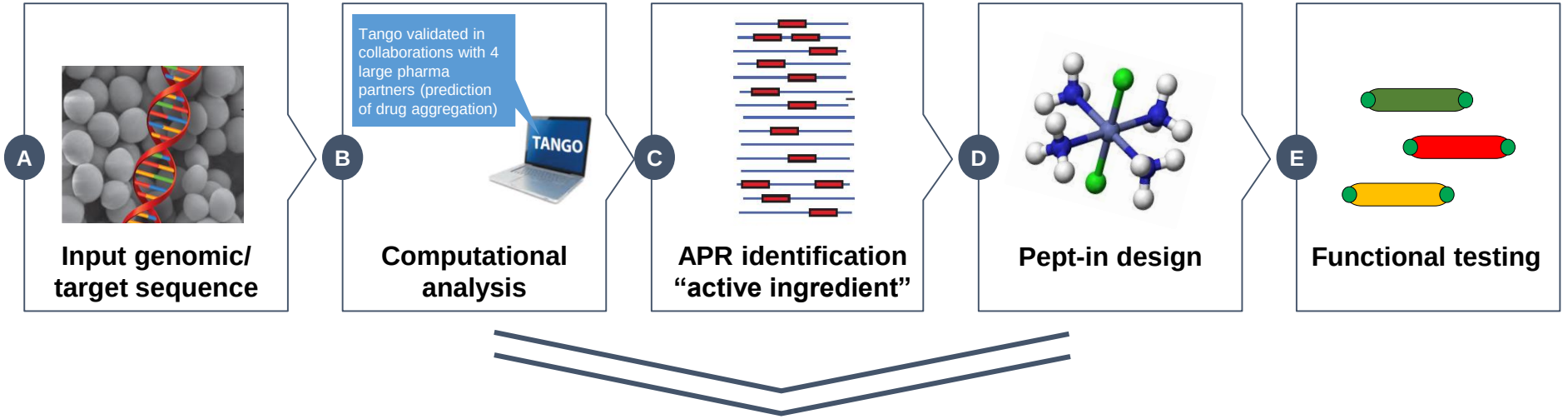
Ventura et al, 2004 PNAS 101 no. 19. 725; Chiti et al, 2003 Nature 425: 805

The Discovery Process



Process covered by granted patents* and pending patent applications covering method of protein interference, use of protein interference and product claims**

*: *US 9,095,556; EP 1962883; CN 101340925; AU 2006326940; CA 2,632,331; IL 192001*
**: *WO2012/12341*: pending in AU, BR, CA, CN, EP, IL, IN, JP, US;
WO2007/071789: still pending in BR, JP, IN

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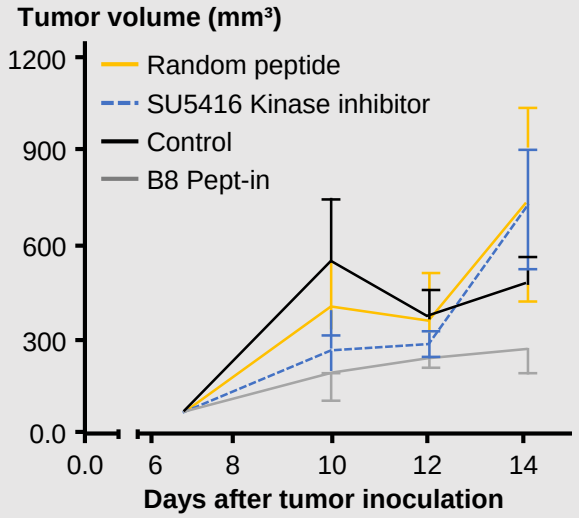
Examples for Successful Applications of technology

Oncology

Pept-in targeting mouse VEGFR2

B16 tumor model for melanoma



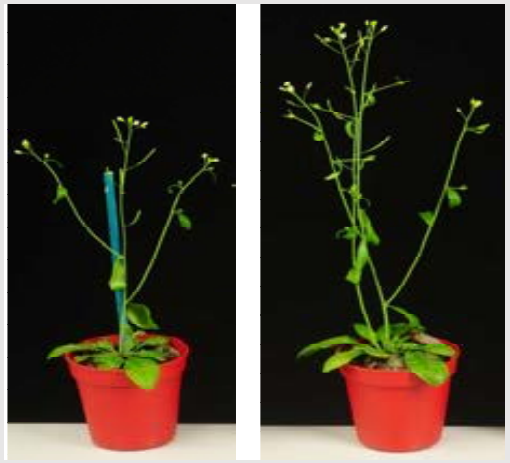
- *Tumor cells (250,000) injected on day 0, treatment on day 3*
- *N = 5 mice per group*

Novel oncology drugs by inhibiting function of growth factor receptors

Agro-Bio

Pept-in targeting plant growth inhibitor

Plant growth model



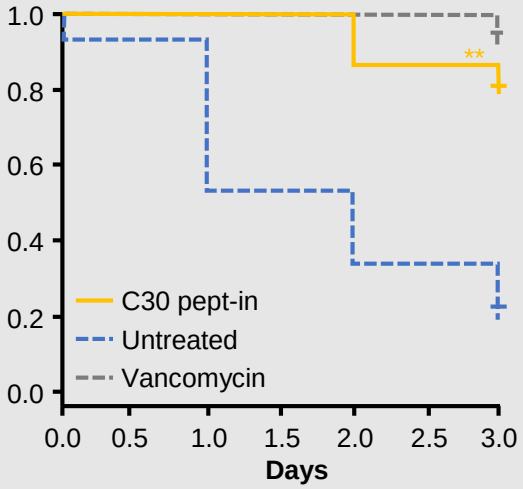
No Pept-in Pept-in

Improved crops by functional knock down of growth inhibitors

Infections

Pept-in targeting proteome of Staphylococcus

Sepsis model Staphylococcus Aureus



- *Mice were inocculated with Staphylococcus Aureus on day 0*
- *Treatment 30 min after inocculation*
- *n = 15 mice per group*

Effective anti-infectives by targeting specific pathogens

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Rationale for use in Bacterial Infections

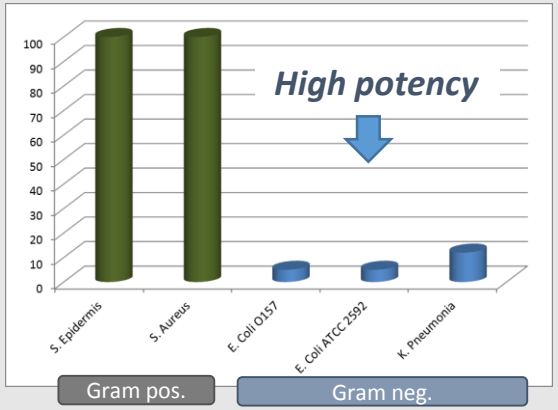
Targeting	• Targeting defined by primary amino acid sequence • Designed to aggregate in target cells • Control over level of cross-reactivity: single vs multiple targets; species specificity	**Specificity**
Mode of action	• Loss of cell function through protein aggregation • Aggregation happens in unfolded proteins → Fast onset of effect in pathogens • Unexplored target space: Any protein can be targeted	**Efficacy**
Membrane crossing	• Charged gatekeeper residues flank the Pept-in active ingredient • Reaching intracellular targets • Ability to target essential intracellular proteins → Prevention of resistance development	**Use in Gram negative infections**

Proof of Concept – Efficacy Bacterial Infections

In Vitro Efficacy leading to …

Low single digit MIC values (ug/ml)

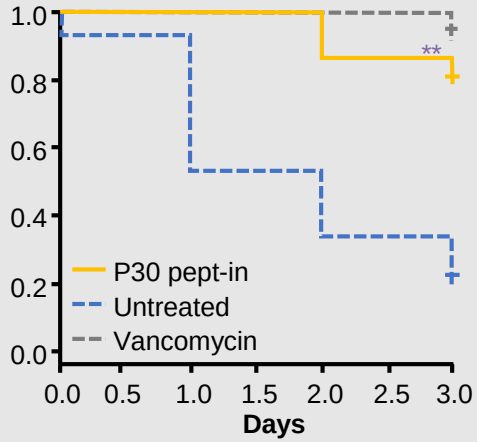
Pept-in designed against gram neg. proteome



…In Vivo Efficacy…

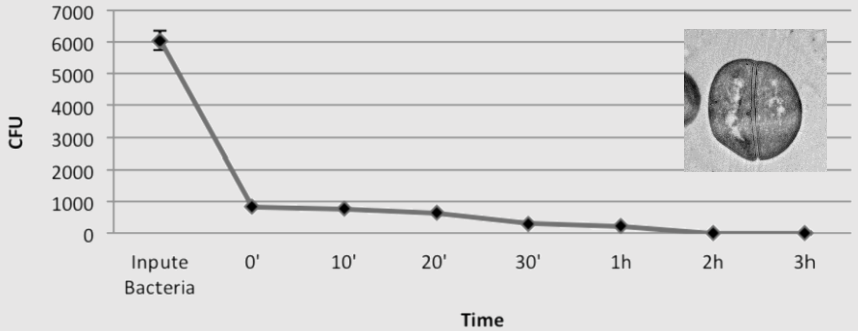
Sepsis model

- Inoculum: *Staphylococcus aureus* MRSA 362
- Treatment i.v. after 30minutes



…fast bacterial killing…

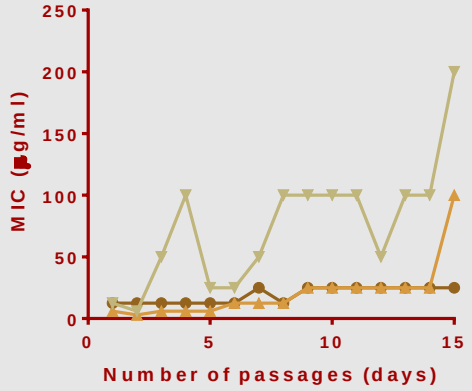
E. Coli (N14 Pept-in)



Fast onset of activity prevents development of resistance

… low resistance build up

repeated passing of MRSA (P30 Pept-in)



In vitro assay shows no resistance development for Pept-in, while Amp/Gent do induce resistance

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POC in Arabidopsis: BRASSINOSTEROID target

Plant steroid hormones

Regulate cellular expansion, proliferation and differentiation

Role in multiple developmental processes

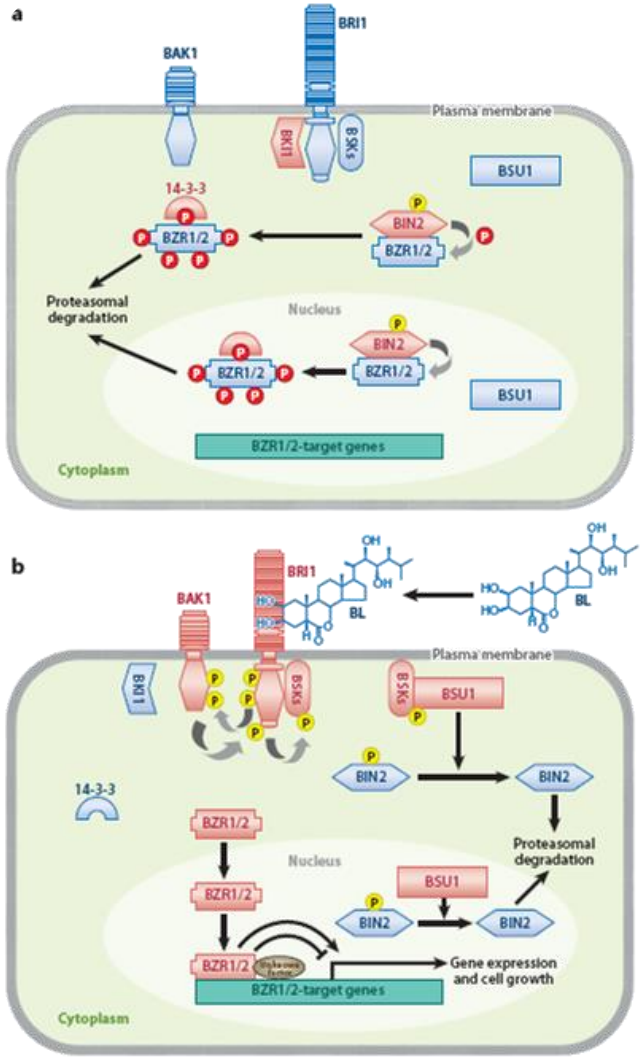
Growth-promoting effect

Selected targets: BRI1, BAK1, BIN2, BES1, BZR1

Focus on **BIN2** kinase
(negative regulator of BR signaling)

Objectives:

- Visualize aggregation in plants
- Target a protein of interest
- Prove the functional knock-out



Kim & Wang, Ann. Rev. Plant Biol. 2010

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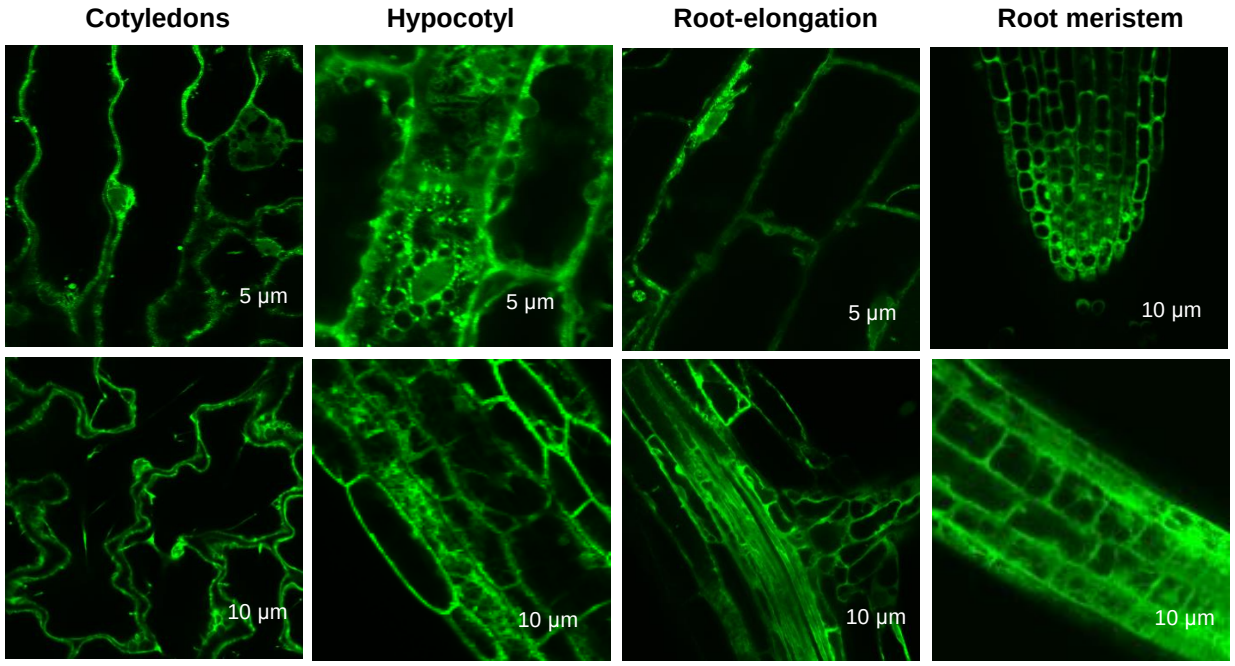
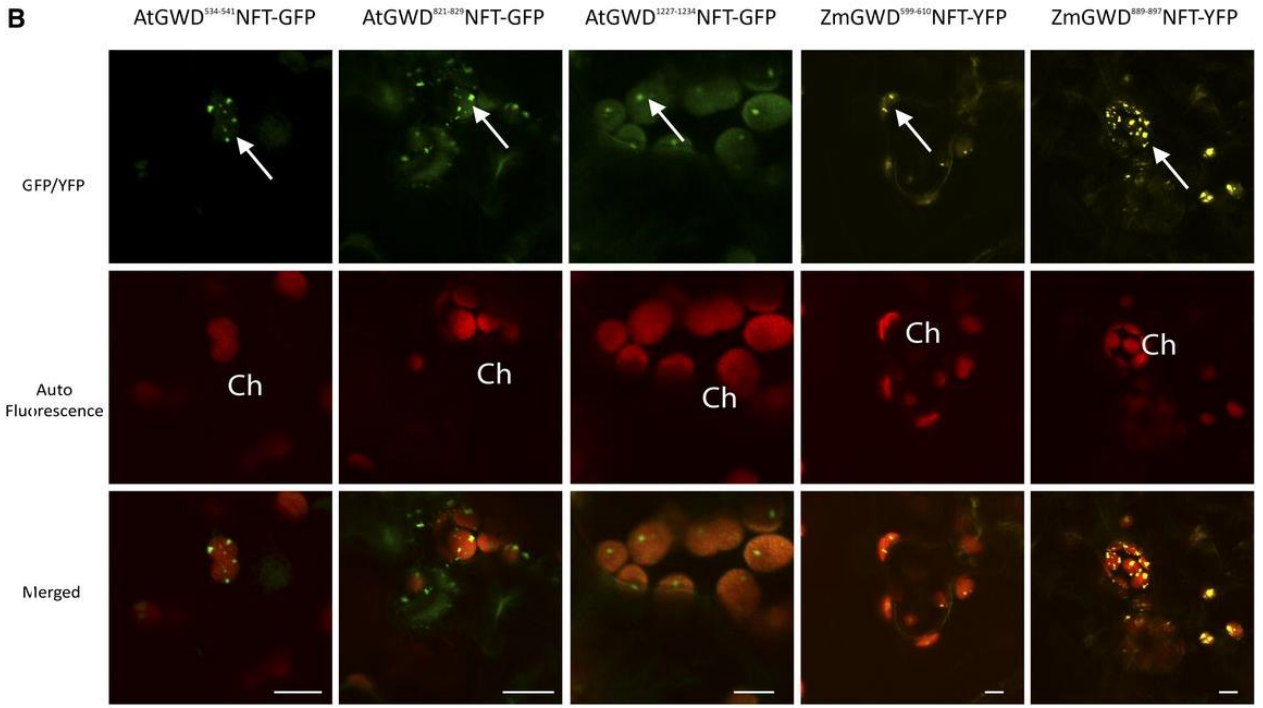
Induction of aggregation in plants

Target: BIN2



Transient expression in Arabidopsis

Target: GWD



Stable expression in Arabidopsis and Zea

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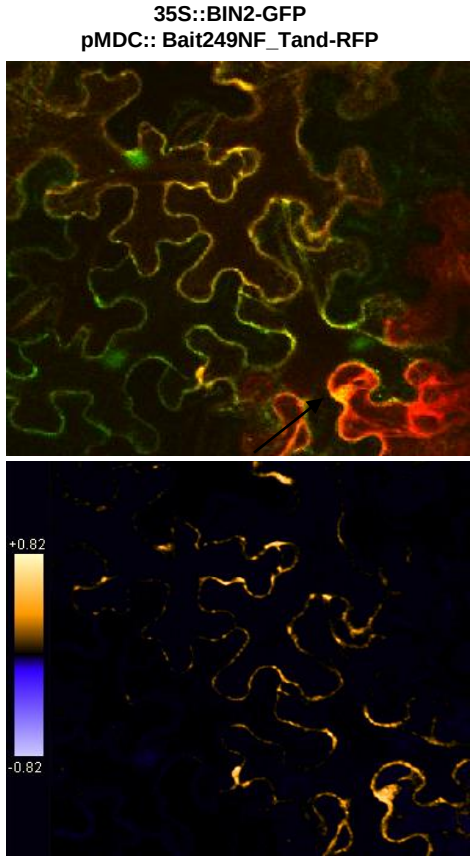
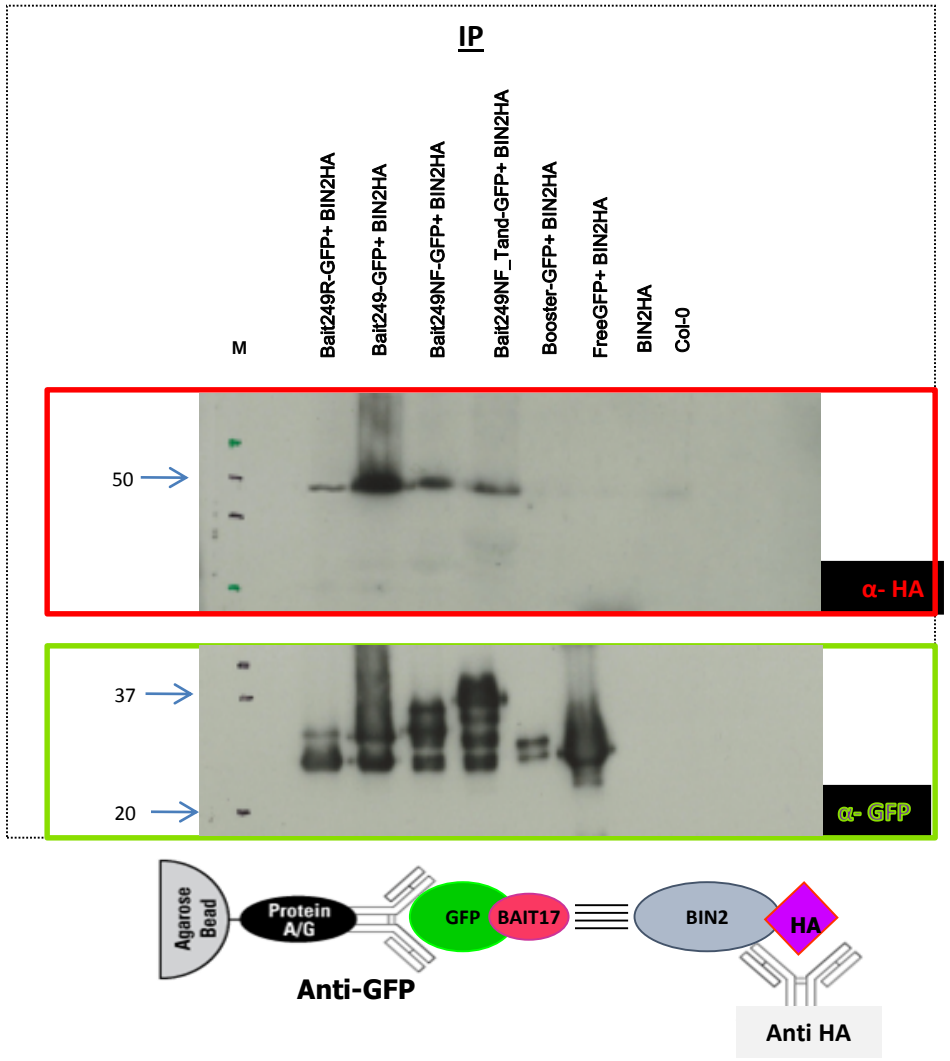
Co-localization and physical interaction in vivo

Transiently transformed *N.benthamiana* leaves





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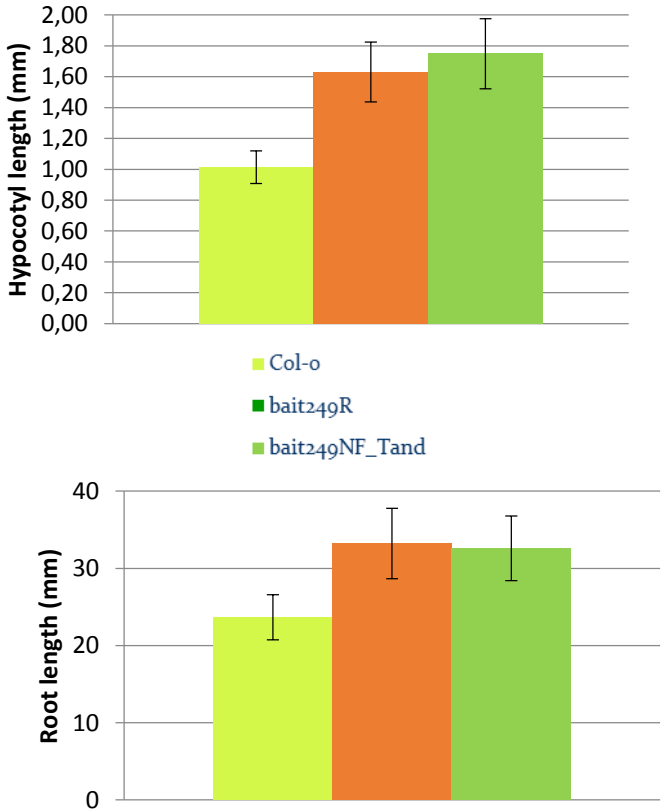
Protein interference in transgenic plants



Protein interferors can be recombinantly expressed in plant cells resulting in a phenotype consistent with specific protein knock-down

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