13 June 2019

In silico tools for the assessment of newly expressed proteins in GMOs

Toxicity

Trusted science for safe food

European Food Safety Authority

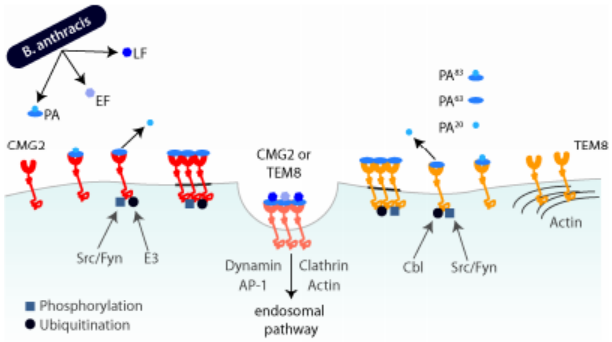
IN SILICO TOOLS - TOXICITY

The present

- The current *in silico* investigations on proteins in GMO dossiers are based on comparisons of the protein sequence to company internal databases

Limitations

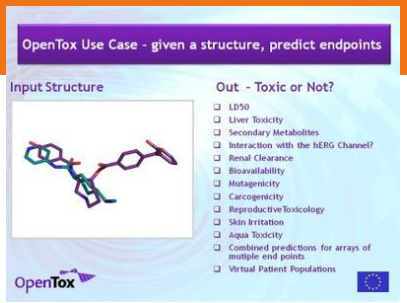
- Sequence similarity cannot be used as sole criterion for defining a protein as a toxin:
  - 3D structures are relevant
  - complex formation
  - specific protein binding/active sites
- Comprehensiveness of databases as regards experimentally validated toxins



Friebe,S et al., 2016 Toxins, 8, 69

Is a better approach possible?
Are there protein predictive toxicity tools useful for GMO RA?

IN SILICO TOOLS - TOXICITY



Predictive protein toxicity tools in RA

Differently from the small molecules area

- no fit-for-purpose tools
- incomplete knowledge on the determinants of pathogenetic effects

The future

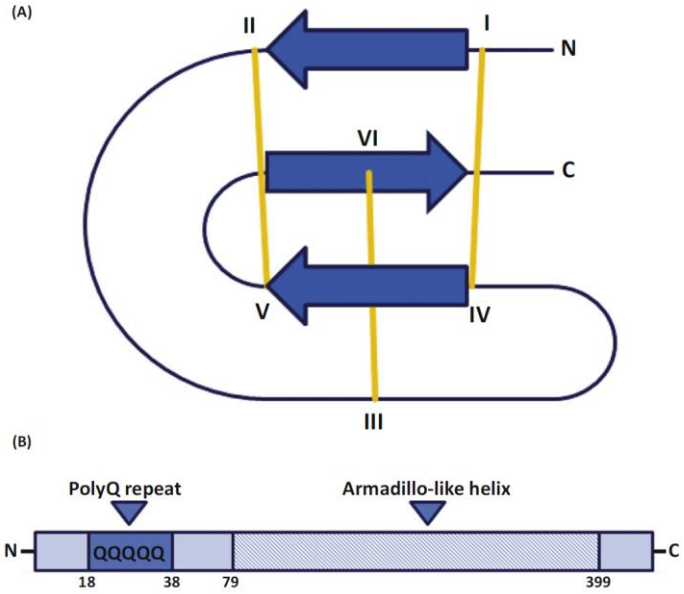
Extensive information is now available in public databases and can serve as the basis for establishing *in silico* tools to determine the potential risk of toxicity

- 3D structures
- protein biological function
- molecular pathways
- molecular signatures

EXAMPLES

Motif analysis

homologous proteins with similar function share similar motifs (critical region relevant for function and folding), even when the overall identity is low (20-30%).



Franceschi et al, 2017
Trends in Biotechnology, 2017, 35, 483

Structural Representation of the (a) Inhibitor Cystine Knot (ICK) and (b) Polyglutamine (polyQ) Motifs.

EXAMPLES

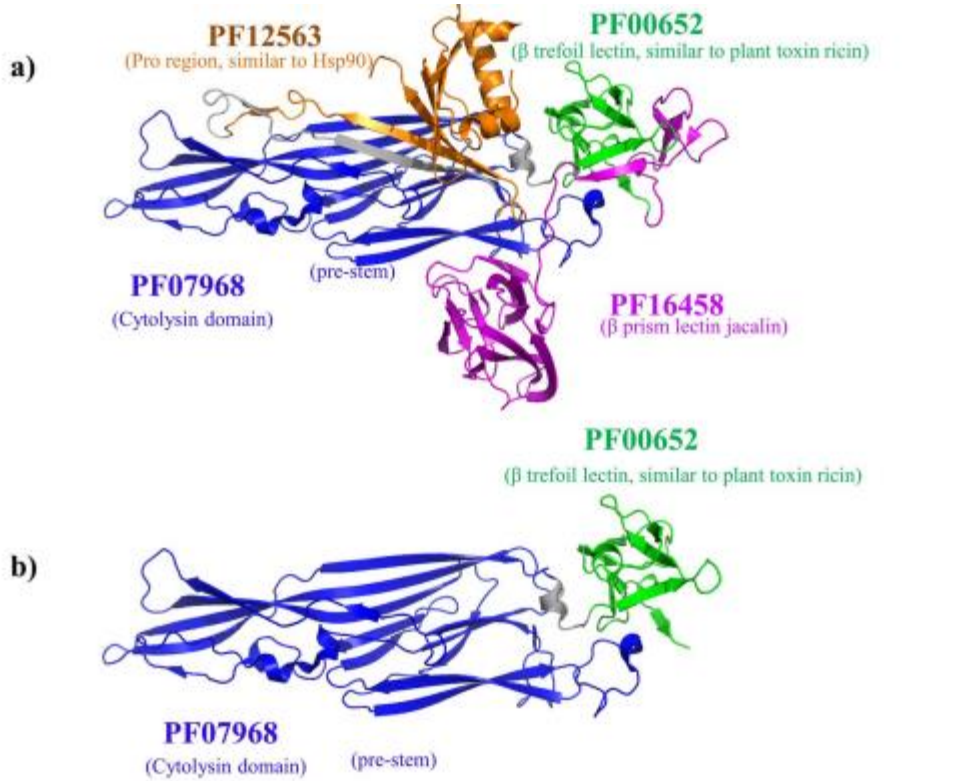


Figure 5. Domain structures of the hemolysins from *Vibrio cholera* (**a**) and *Vibrio vulnificus* (**b**). The membrane-active form of both is a heptameric, pore-forming structure.

Negi et al, 2017
Scientific Reports 7: 13940

NP/EFSA/GMO/2018/01

Literature search – Exploring in silico protein toxicity prediction methods to support the food and feed risk assessment

1. identifying, list and cluster proteins known to be associated with adverse effects in humans and animals
2. to identify molecular signatures (e.g. motifs, domains) of these "toxic" proteins and the pathogenesis leading to adverse effects in humans and animals.
3. to identify available databases and evaluate their relevance with respect to the scope.

Deadline Jan 2020

- Is there any similar exercise currently undertaken or planned by Europabio?

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