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Biological Properties and Production of Tetanus Toxin Fragment C: An Update on Literature from 2010 to Present

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Introduction

Tetanus toxin fragment C (TTFC) is non-toxic and has highly promising biological properties (Toivonen et al 2010), notably in immunology and neurology (Herrando-Grabulosa et al 2020, Calvo et al 2012). TTFC is able to trigger an immune response, so it can be fused with tumoral or pathogen components to produce efficient anti-cancer and anti-infectious vaccines.

Moreover, TTFC crosses the blood-brain barrier → it is studied as vector for drugs against neurological disorders. Its intrinsic neuroprotective properties constitute a hope to treat neurodegenerative diseases.

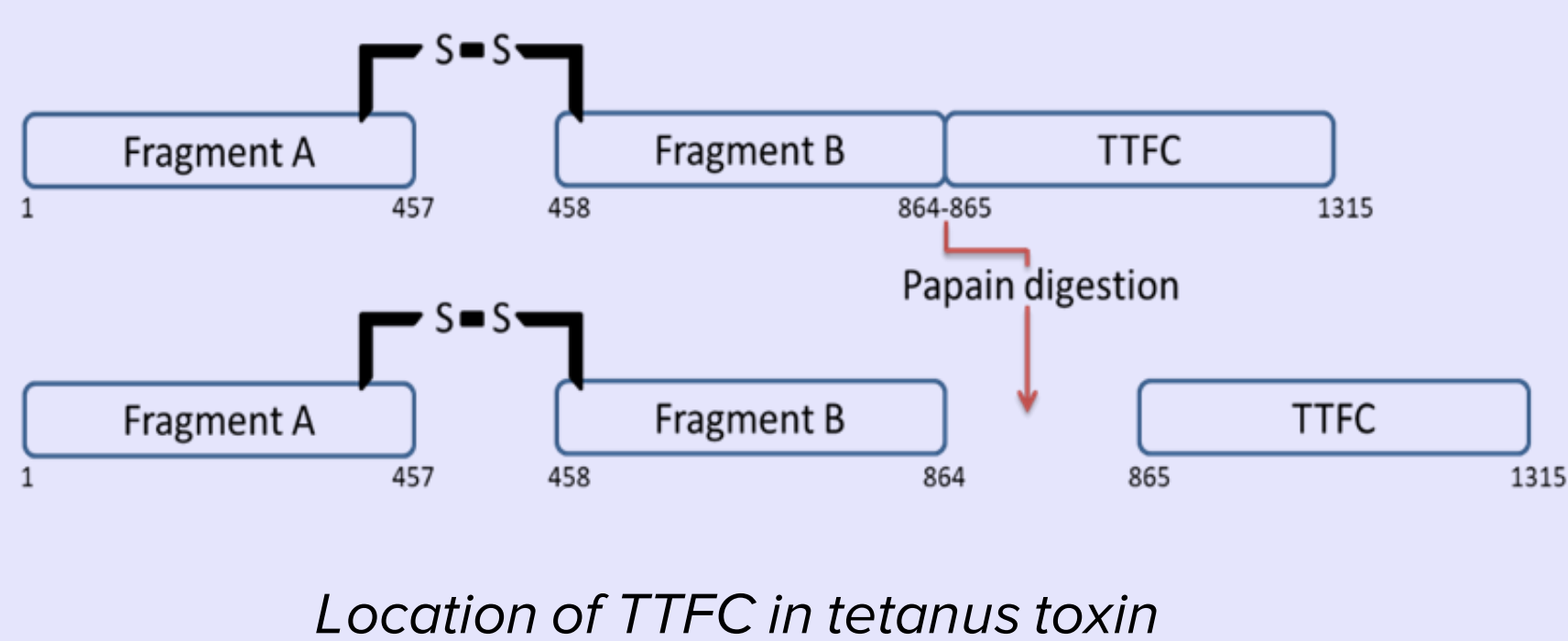
Different production methods have been developed, notably in recombinant systems like *Escherichia coli*.

This communication aims to update knowledge about TTFC from 2010 to 2022.

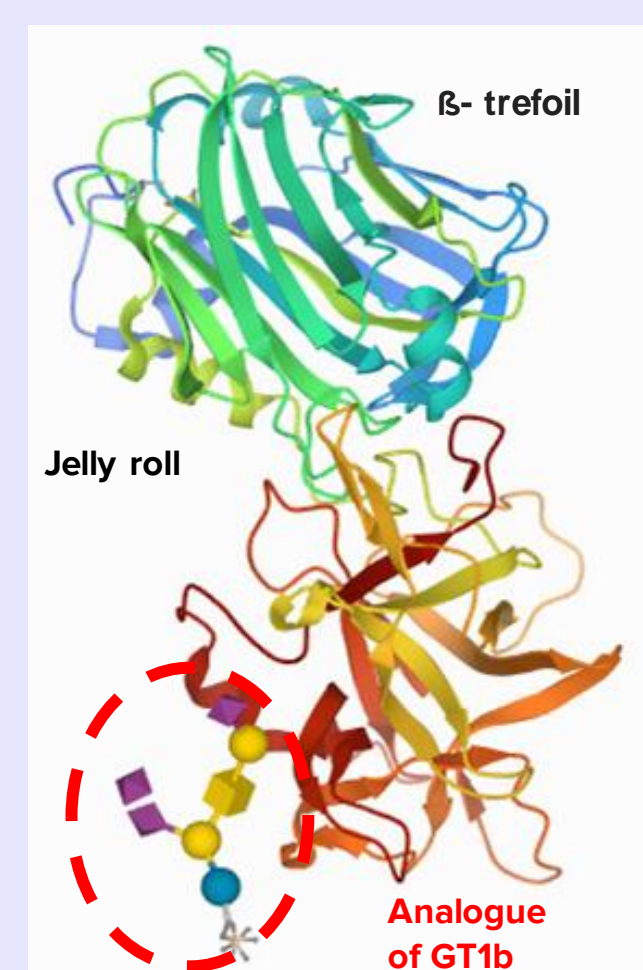
Structure of TTFC

7 X-ray structures were found in the Protein Data Bank.

- Tetanus toxin is secreted by the bacteria *Clostridium tetani*
- Tetanus toxin: 150 kDa. TTFC : 52 kDa.
- TTFC is located at the C terminus of the tetanus toxin's heavy chain.



Fotinou et al., J Biol Chem, 2001



TTFC complexed with an analogue of its ganglioside receptor GT1b

Query of several databases:

- PubMed, Web of Science and Scifinder-n for articles
- Protein Data Bank (PDB) for molecular structures
- Esp@cenet for related patents

Global literature search equation:
 ("tetanus toxin fragment c" OR "tetanus toxin c fragment" OR "tetanus toxin Hc fragment" OR "fragment C of tetanus toxin" OR "Hc fragment of tetanus toxin")

between 2010 and 2022

→ All main TTFC synonyms are covered by the equation

Use of Zotero to identify duplicated articles between databases.

Terms and abbreviations used to refer to TTFC

Tetanus toxin fragment C	TTFC or TTFrC or TtxFC
Tetanus toxin C fragment	TTCF or TTC or TetC or TCF
Tetanus toxin heavy C fragment Non-toxic carboxylic fragment of tetanus toxin	TeTx H _c or H _c -TeTx
Tetanus toxin native heavy C-fragment	TeNT-Hc
C-terminal fragment of tetanus toxin Fragment C of tetanus toxin	FrgC or FrC

From the global equation, three additional equations were formulated:

Production: Global equation AND (produ* OR prepar* OR express*)

Neurological uses: Global equation AND (neuro* OR brain)

Immunological uses: Global equation AND (immunology OR immunogenicity)

Results and discussion

TTFC: Global results

102 articles on PubMed (PM), 81 on Web of Science (WoS) and 109 on Scifinder-n (SF)

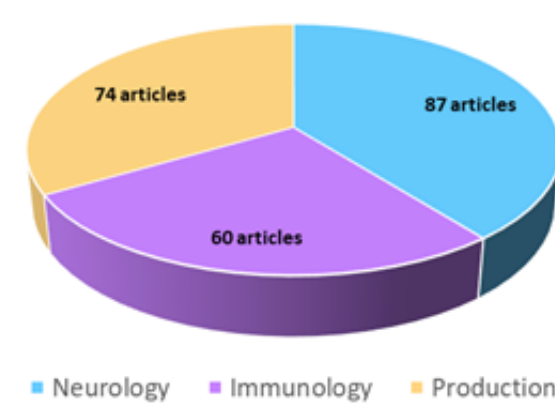
Comparison of results from PM and WoS: 9 articles from WoS were not found on PM

→ Importance to browse multiple databases.

→ Need of a tool like Zotero to sort articles and remove duplicates.

→ PM and SF seemed more powerful than WoS for this subject, as WoS is specialized in chemistry while PM and SF also cover biomedicine and health engineering.

Topic repartition of articles about TTFC found on PubMed and/or WoS (total = 113 articles)



Neurological uses

78 articles on PM, 29 on WoS and 86 on SF
 → broad differences between databases

Examples of neurological uses of TTFC

Medicinal product	Biological interest	Reference
TTFC <i>alone</i>	Alzheimer's disease	Patricio-Martínez et al, Neuroscience 2016
TTFC <i>fused</i> with GDNF (neurotrophic factor)	Amyotrophic lateral sclerosis	Moreno-Igoa, Restor. Neurol. Neurosc. 2012
TTFC <i>conjugated</i> with radioactive iodine	Exploration of retrograde transport in spinal cord	Lee et al, Ann. Neurol. 2022

Immunological uses

57 articles on PM, 20 on WoS and 23 on SF

Examples of immunological uses of TTFC

Medicinal product	Targeted disease	Reference
TTFC <i>alone</i>	Tetanus	Luo et al, Vaccines 2012
TTFC <i>fused</i> with <i>S. aureus</i> coagulase	<i>Staphylococcus aureus</i> infection	Qian et al, Microbes Infect. 2019
TTFC <i>conjugated</i> with Her2 fragment	Her2+ breast cancer	Chotprakaikiat et al, Oncoimmunology 2016

Production of TTFC

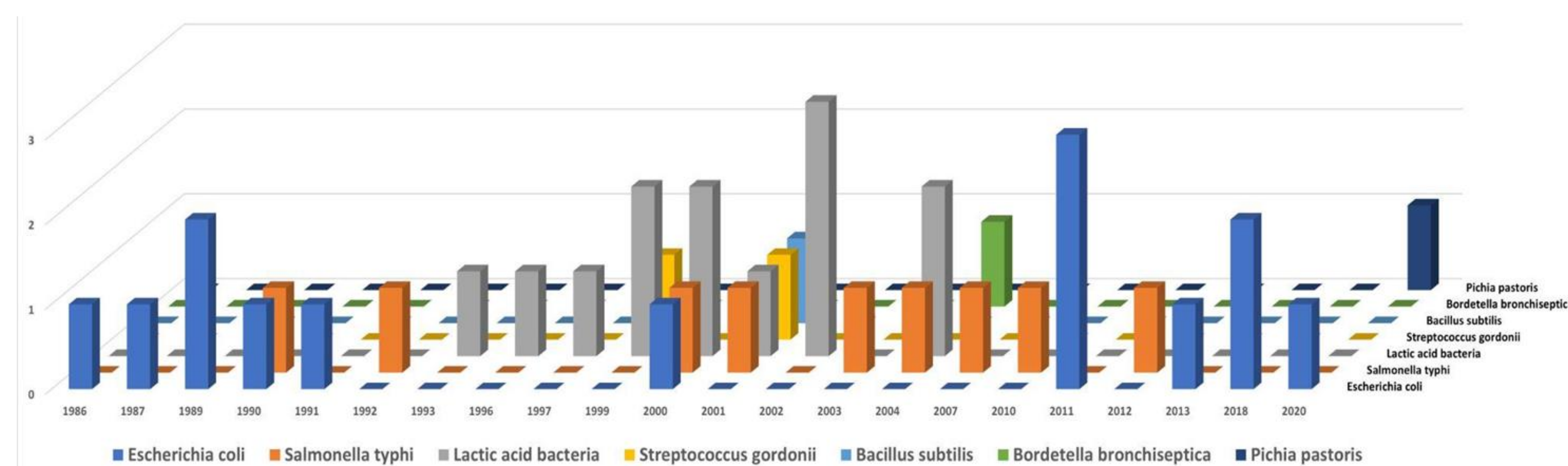
59 articles on PM, 52 on WoS and 83 on SF
 → again, relevance to browse SF

Before 1986: TTFC could only be obtained via digestion of tetanus toxin by papain → dangerous to manipulate the toxin, and low yield (about 20%).

Since 1986: emerging of recombinant systems to produce only TTFC → safer and more efficient.

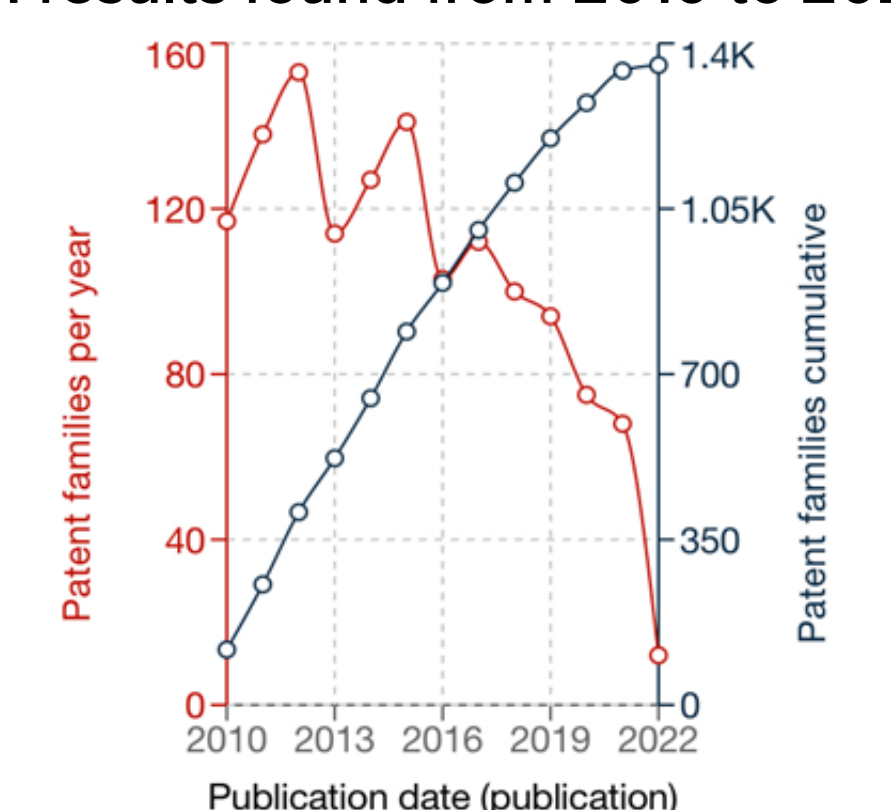
Original recombinant system: *E. coli*

Distribution of the expression systems for bacterial production of TTFC over the years



Esp@cenet

331 results found from 2010 to 2022:



A recent patent:
 Univ Howard, c-terminal fragment of tetanus toxin (HC) for treatment of depression, US2021361739A1, 2021.

Conclusion

- TTFC shows promising results to prevent and treat neurological diseases like Alzheimer's, alone or as a carrier.
- TTFC can be also used to increase immunogenicity of vaccines against bacteria (e.g. *Staphylococcus aureus*) and cancers (e.g. lymphoma).
- Due to this rising interest, innovative production systems are being developed, especially in bacteria like *S. typhi* and *P. pastoris*.

- A review article is in preparation to update knowledge about TTFC since the last major review (Toivonen et al, 2010). It will be submitted to *Pharmaceuticals*.
- This literature search enabled us to put into practice our pharmaceutical education, notably about bibliography, molecular biology, pharmacology, and bioinformatics.