

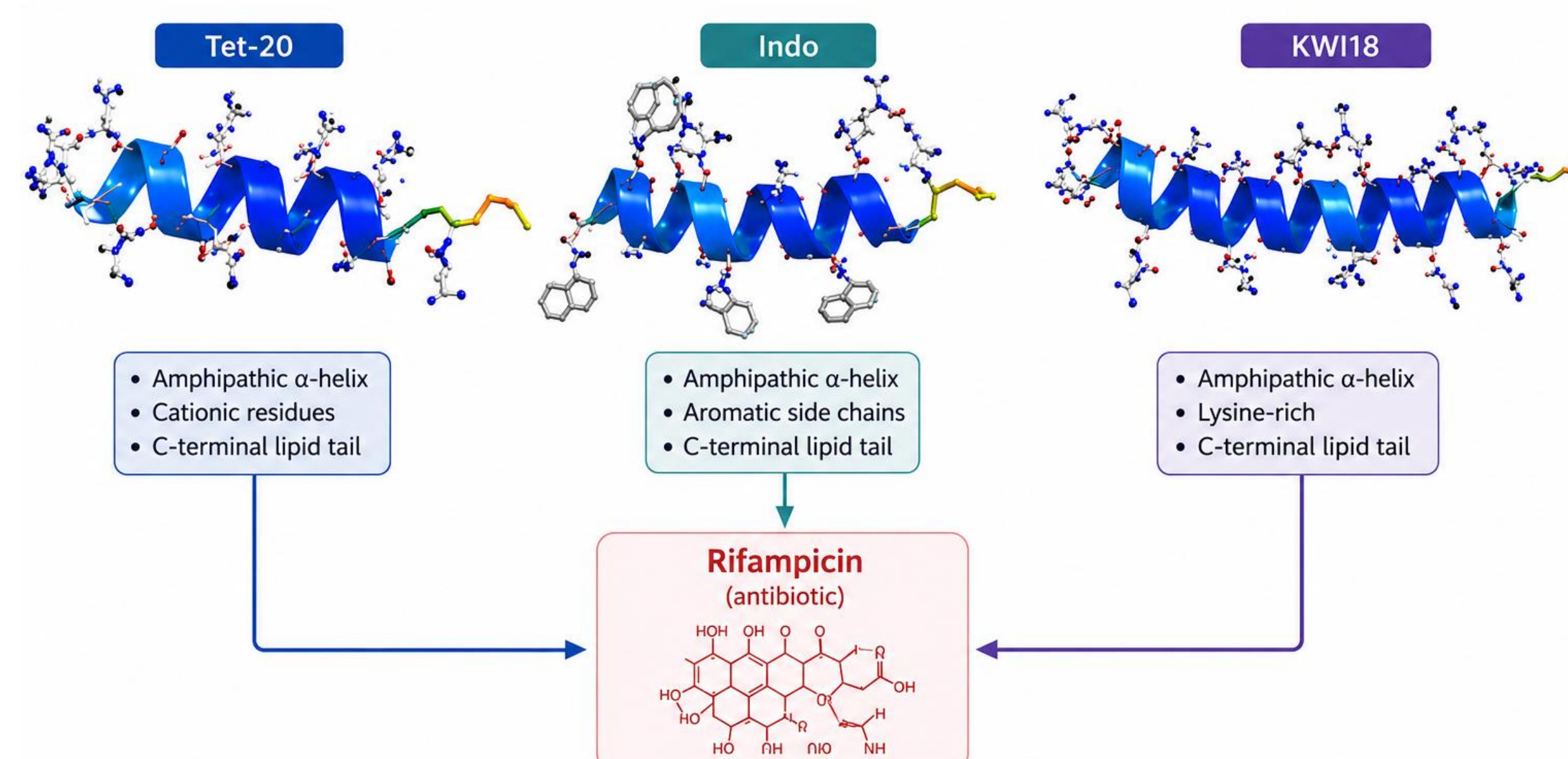
Evidence of *in vitro* and *in vivo* synergy between rifampicin and antimicrobial peptides in implant-related infections

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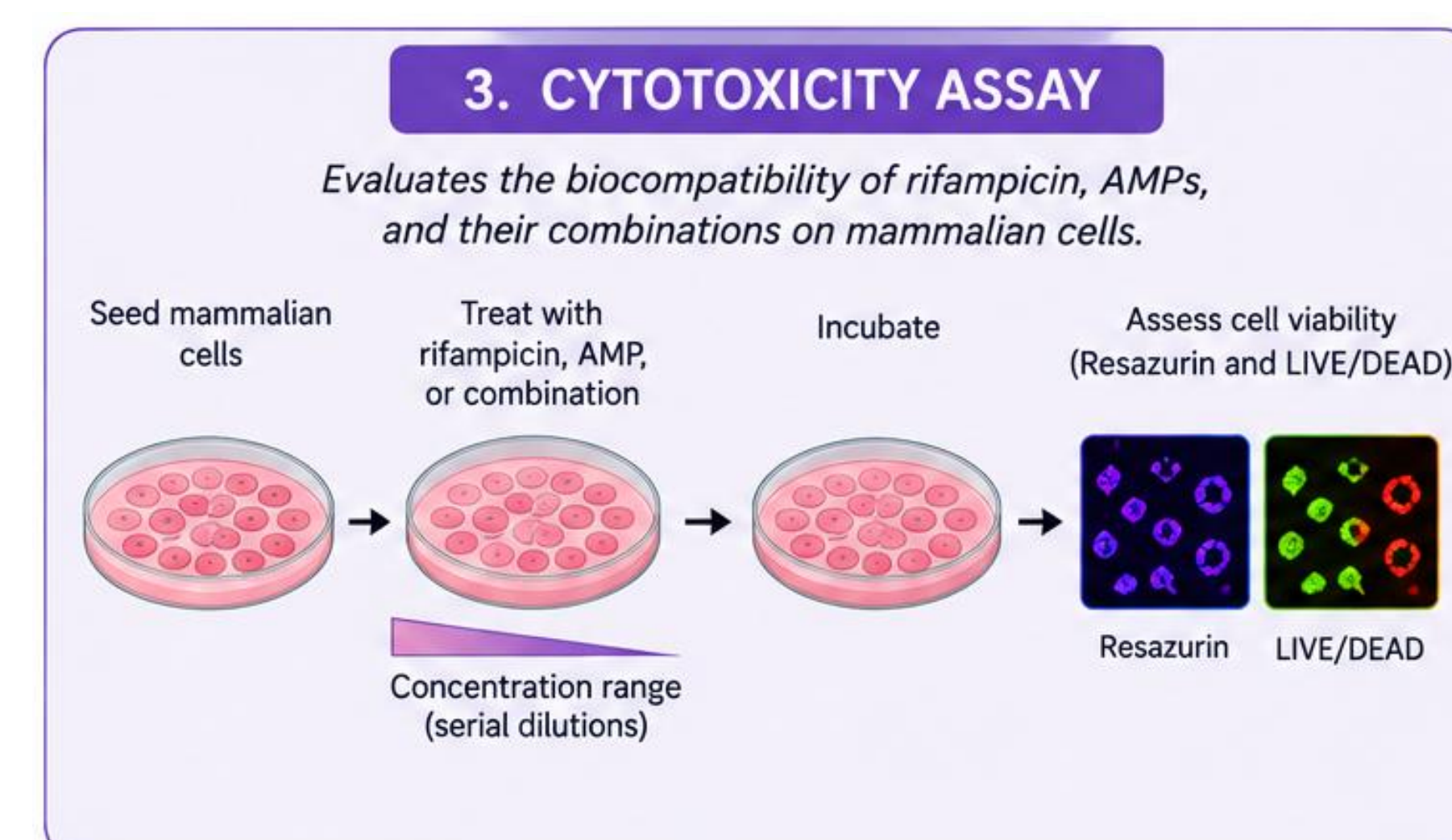
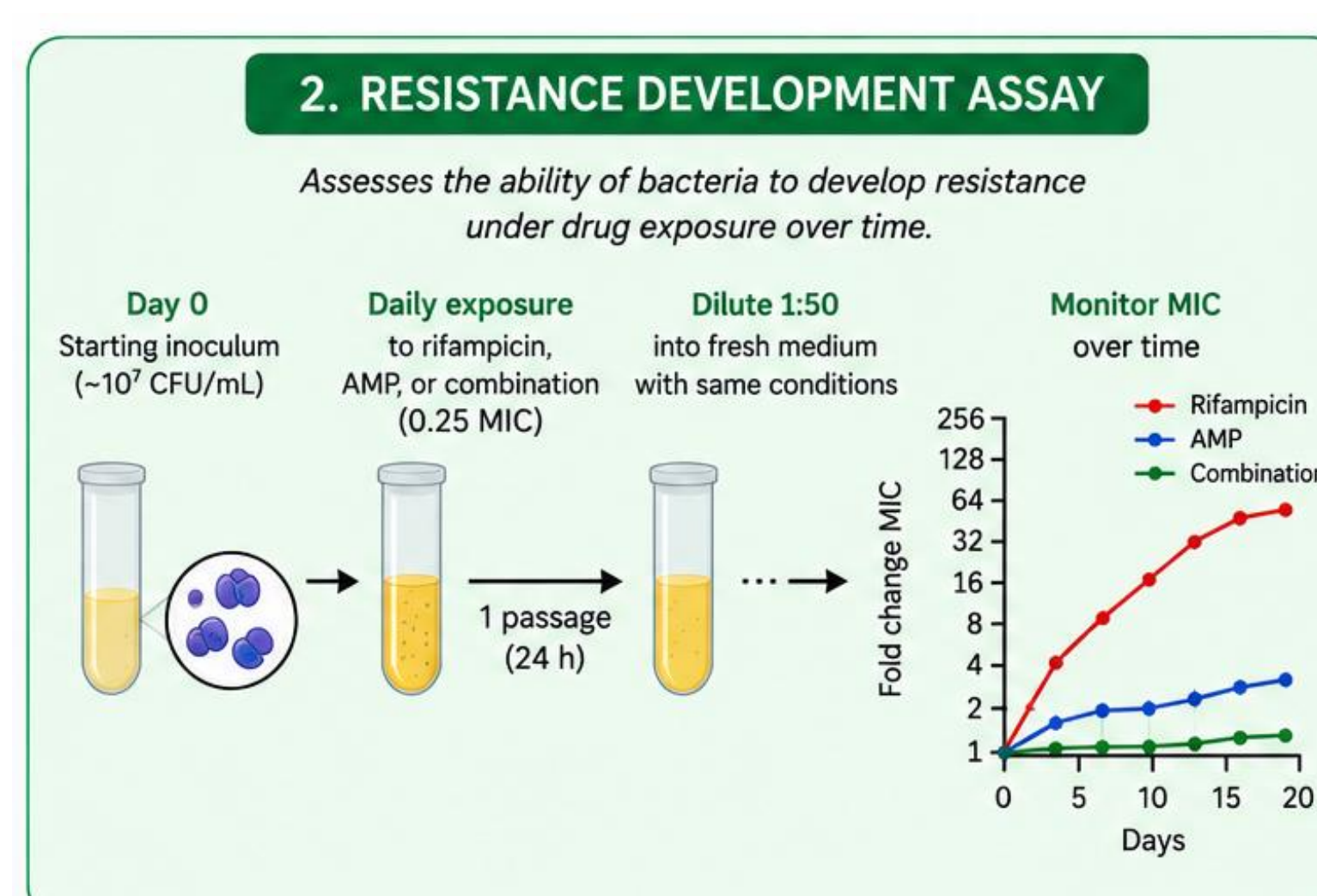
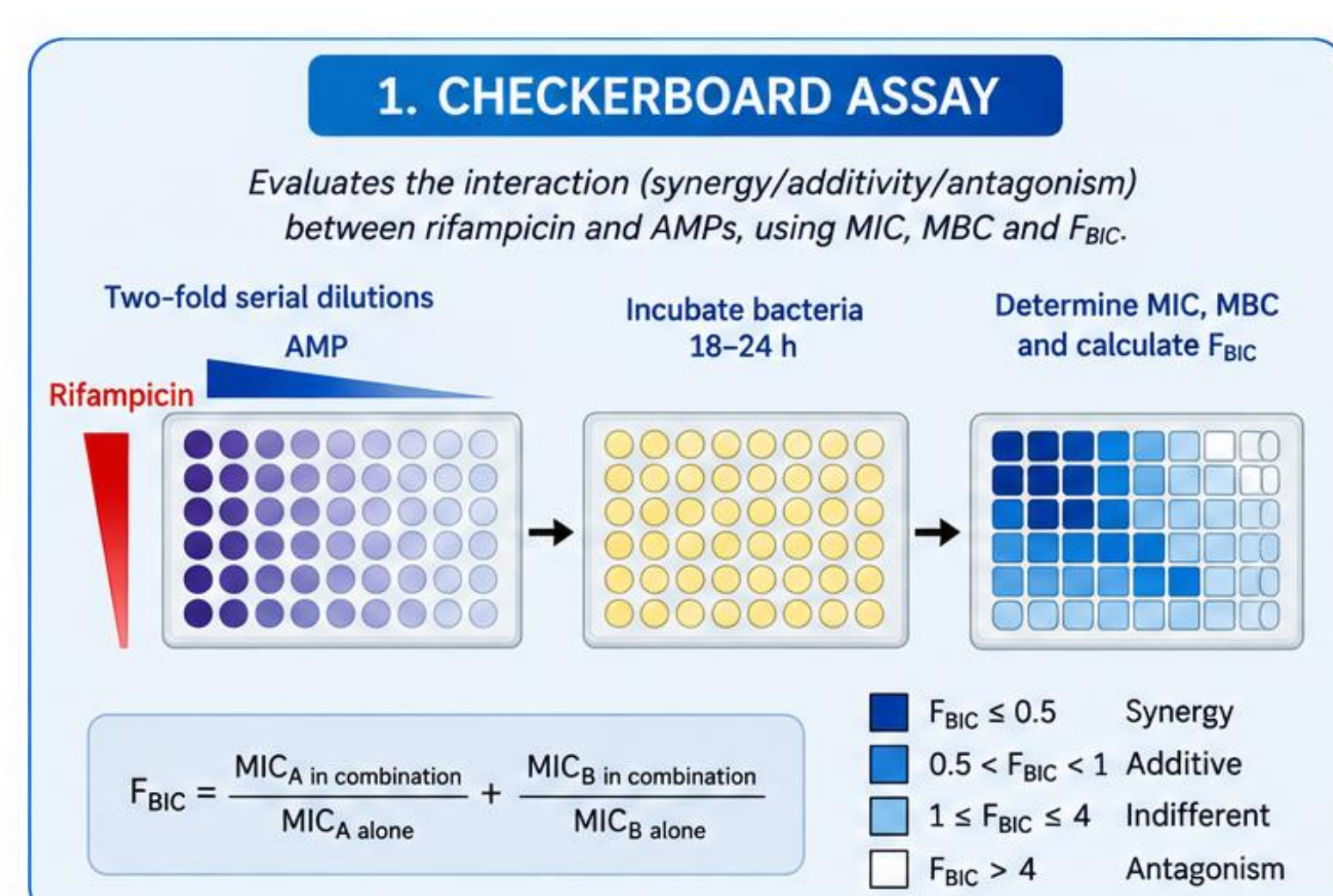
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Antimicrobial peptides for treating orthopaedic infections

- Biomaterial-associated infections (BAIs) are a major complication for trauma patients.
- Approximately 33% of musculoskeletal infections are caused by *Staphylococcus aureus*.
- Rifampicin-based combination therapies are recommended for early-diagnosed BAIs.
- However, the emergence of rifampicin resistance may compromise treatment efficacy.
- Combining antimicrobial peptides (AMPs) with rifampicin represents a promising therapeutic strategy, although these combinations have not yet been evaluated in clinical studies.
- We aim to evaluate the short- and long-term efficacy and biocompatibility of rifampicin-AMP combinations using *in vitro* and *in vivo* models.



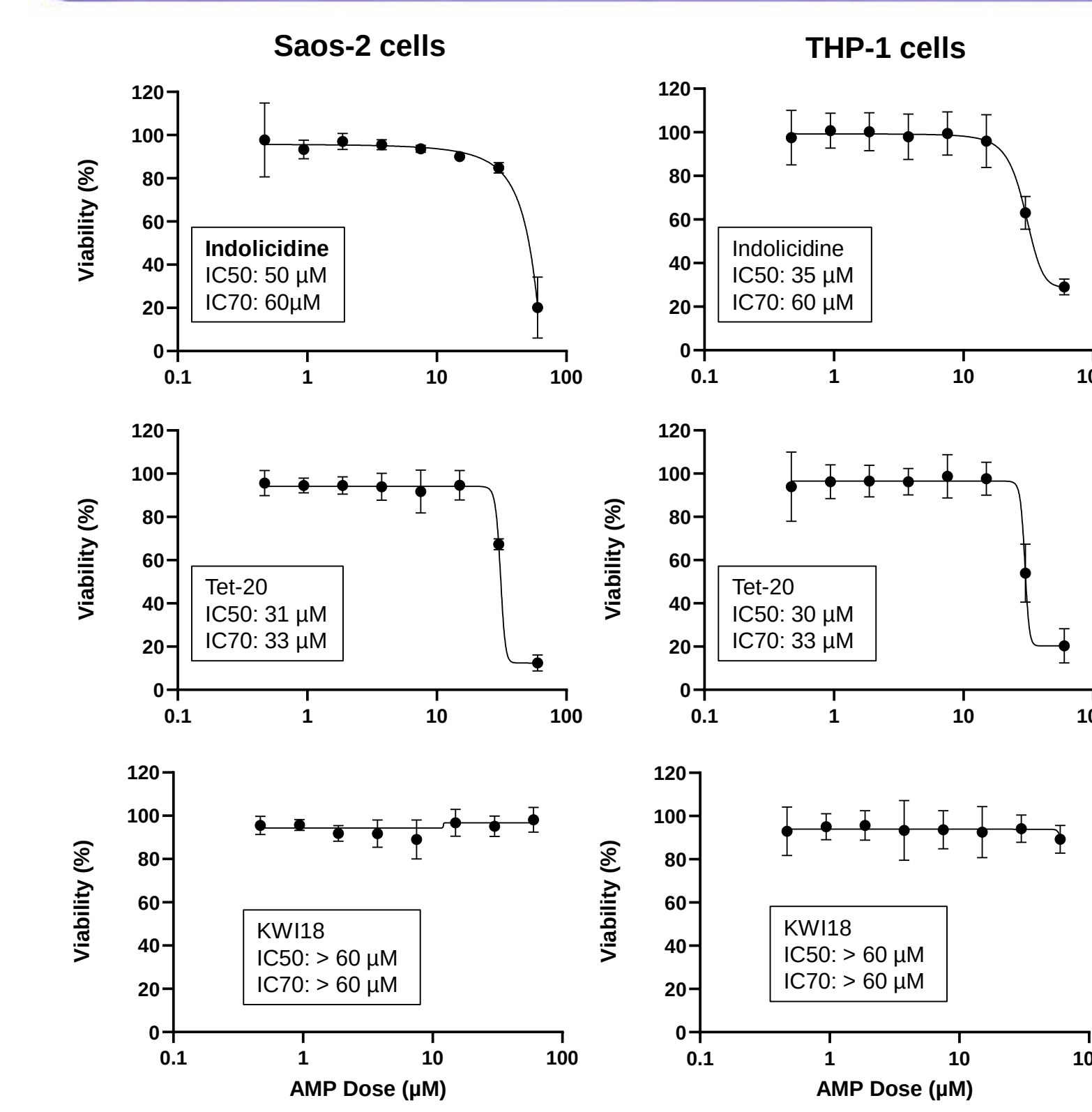
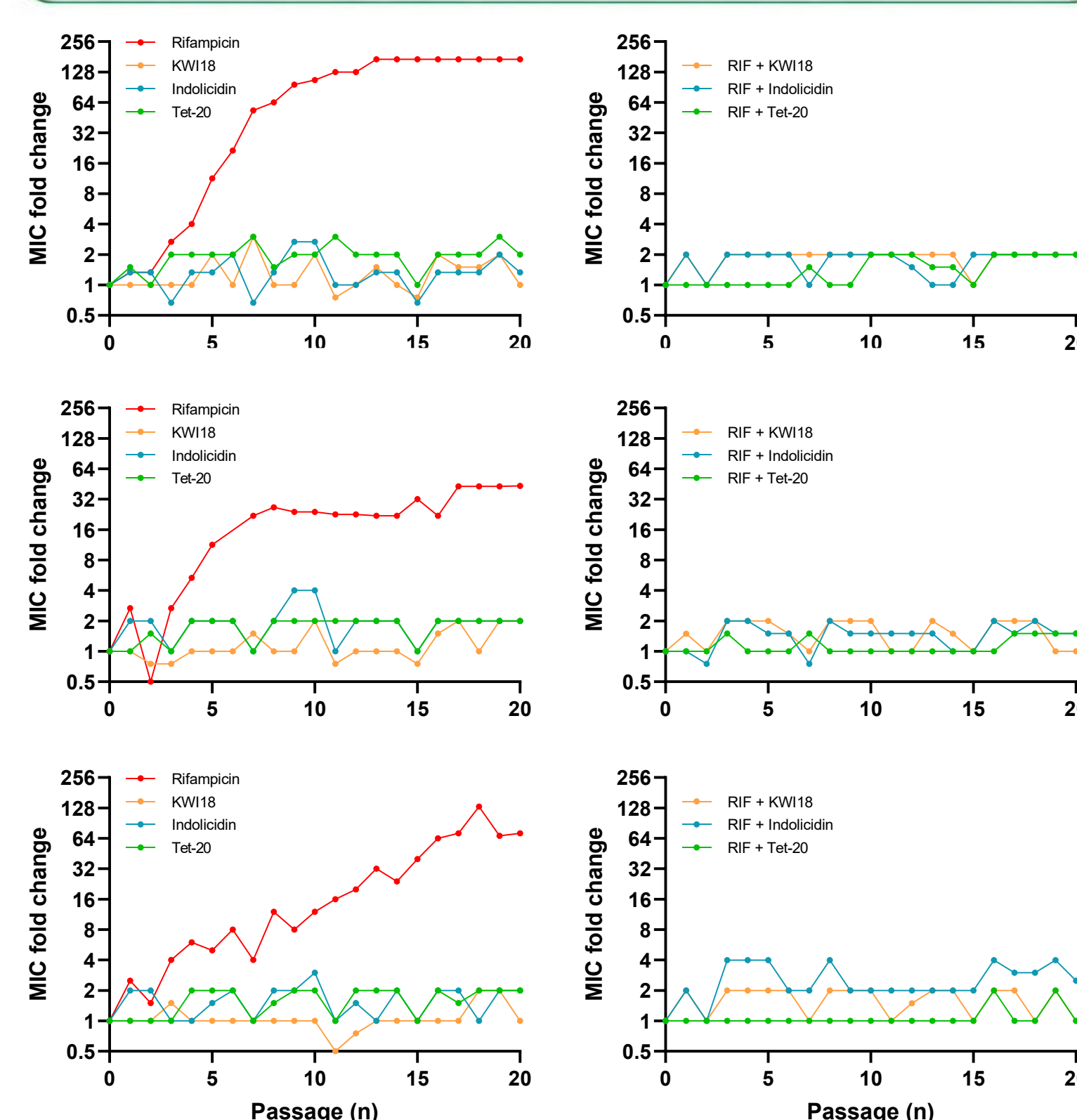
Long-term efficiency and biocompatibility of Rifampicin-AMPs combinations



JAR 060131											
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MBC
Alone	128	3.8	256	3.8	128	7.5	128	15	128	7.5	256
Combined	64	0.9	64	3.8	32	0.9	32	7.5	64	0.9	64
Fold red	2.0	8.3	8.0	3.95	4.0	8.3	4.0	2.0	8.3	4.0	16.6
FICI	0.62	0.38	0.37	0.75	0.62	0.31					

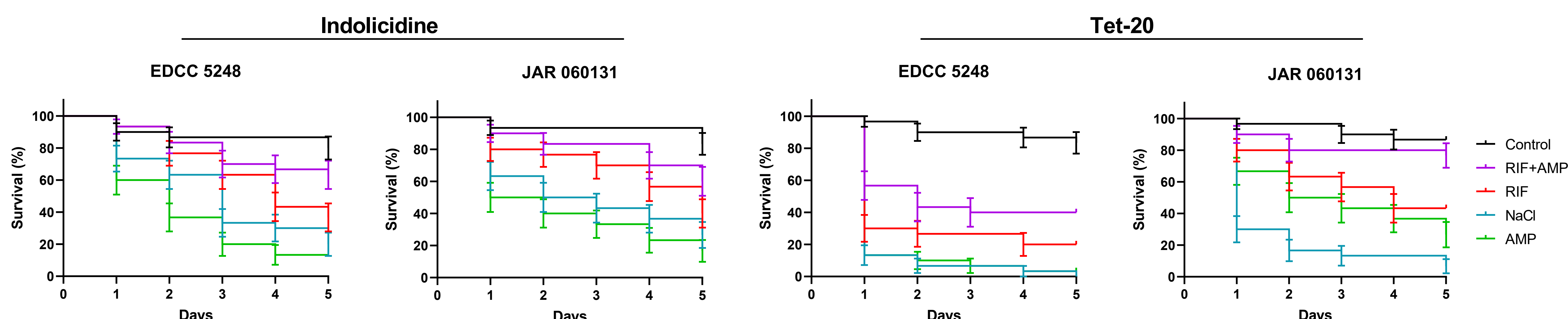
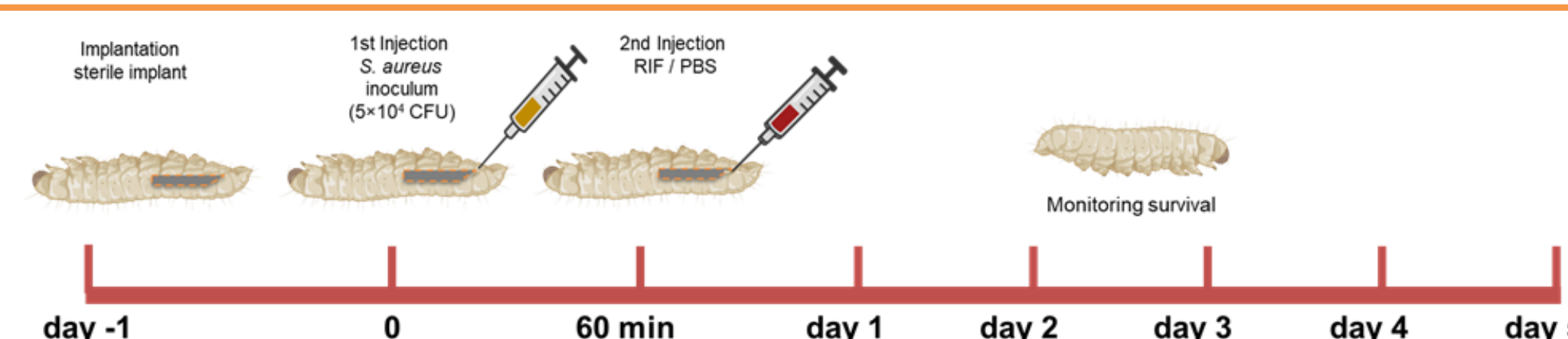
EDCC 5248											
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MBC
Alone	128	3.8	256	3.8	128	7.5	128	15	128	7.5	256
Combined	32	0.9	64	3.8	32	0.9	32	7.5	64	0.9	64
Fold red	4.0	4.2	4.0	4.2	8.0	3.8	4.0	7.6	8.0	3.8	7.6
FICI	0.49	0.49	0.39	0.39	0.39	0.62					

EDCC 5055											
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MBC
Alone	128	3.8	256	3.8	128	7.5	128	15	128	7.5	256
Combined	8	1.9	64	0.9	32	0.9	32	7.5	64	0.9	64
Fold red	8.0	2.0	4.0	4.2	2.0	2.1	2.0	4.2	32.0	2.0	4.0
FICI	0.62	0.49	0.37	0.75	0.53	0.75					



Antimicrobial efficiency assessed *in vivo* in *G. mellonella*

Haematogenous infection model in *G. mellonella* larvae



Conclusions

- Rifampicin-AMP combinations show enhanced antimicrobial efficiency compared with single-agent treatments ($FICI/FBIC \leq 1$ for 3/3 *S. aureus* clinical strains).
- Occurrence of rifampicin resistance is reduced by combining this drug with AMPs.
- The AMPs are well tolerated by human cells (THP-1 and Saos-2 cells).
- The AMPs are non-toxic in *G. mellonella* larvae (100% survival 5 days post-injection; data not shown).
- The Rifampicin-Indolicidine or Tet-20 based therapies increase significantly the survival rate compared with single treatment.

Perspectives

- Rifampicin-AMPs interactions are investigated to better understand how the combined treatment potentialises rifampicin antimicrobial efficacy.
- Antibiofilm assays on metallic implants are planned to valorize the treatment for treating hard-to-treat infections.

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