MULTI-TARGET BACTERIAL GENE THERAPY FOR CHRONIC WOUNDS AND CANCER

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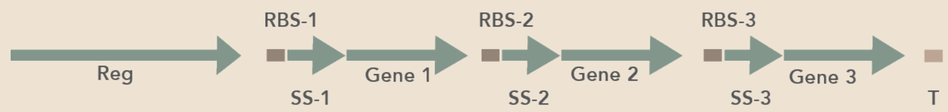
INTRODUCTION

Complex diseases like chronic wounds and cancers are multi-factorial. Unfortunately, existing treatments are unable to address multiple biologic targets. Aurealis' platform and gene therapy products are uniquely suited to address those needs. Aurealis' 4-in-1 products can be deployed directly at the site of the disease, delivering multiple therapeutic factors - cytokines, chemokines, growth factors, antibody fragments... - adapted to a specific indication. This allows very high efficacy, a clear regulatory pathway - multiple factors in one API - and substantially lower manufacturing costs versus other treatment types such as CAR-T or viral vectors. In this poster we show the development and high clinical efficacy of this approach for chronic wounds - such as diabetic foot ulcers - and preclinical data for ovarian and peritoneal cancer.

Host: *Lactococcus cremoris* non-pathogenic, transient and with immune-activating properties.

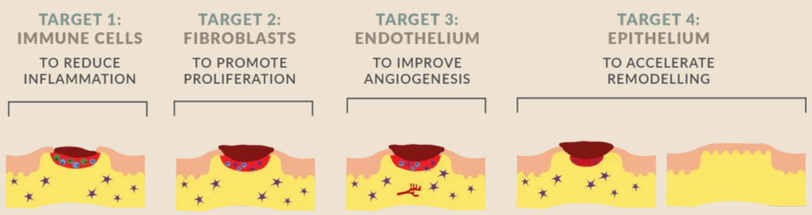
Constructs: Making use of procaryotic genetic elements to design operons consisting of an inducible promoter (Reg), signal sequences (SS), internal ribosome binding sites (RBS), the human target genes and a terminator (T).



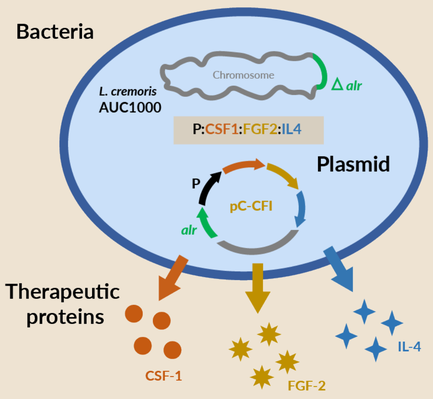
AUP-16 FOR CHRONIC WOUNDS

DIABETIC FOOT ULCER

MODE OF ACTION



CONSTRUCT

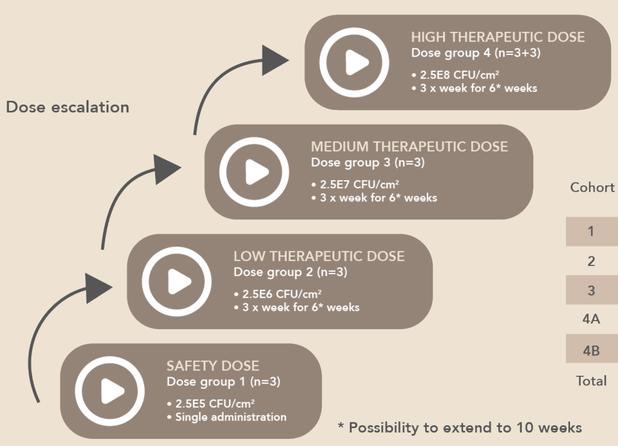


Lactococcus cremoris AUC1000	Genetically engineered strain for food-grade plasmid selection
Δalr	Food-grade plasmid selection; host strain cannot grow without the plasmid
alr	Food-grade plasmid selection without antibiotic resistance gene
FGF-2	Enhances wound healing by increasing migration and proliferation of fibroblasts & keratinocytes, increase granulation tissue formation and improving vascularization
IL-4	Enhances wound healing by suppressing acute inflammation and M2 polarization of macrophages
CSF-1	Enhances wound healing by M2 polarization of macrophages and recruitment of progenitor cells

MANUFACTURING

GMP manufacturing for clinical trials in a sterile, single-use closed system to ensure a monoseptic product.

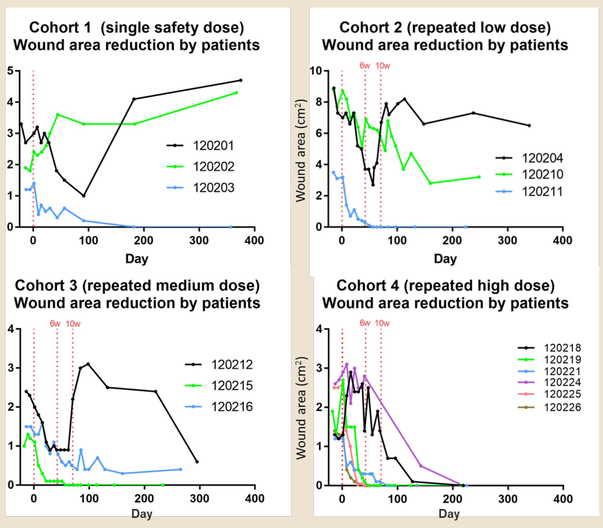
PHASE 1 CLINICAL TRIAL



* Possibility to extend to 10 weeks

RECRUITMENT

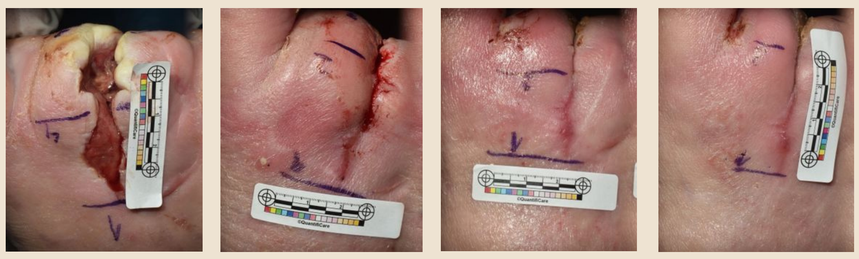
Cohort	Screened	Screening failures	Randomized	% SF	Complete DLT period	Dropouts	% Dropouts
1	3	0	3	0.0	3	0	0.0
2	8	5	3	62.5	3	0	0.0
3	5	1	4	20.0	3	1	33.3
4A	5	2	3	40.0	3	0	0.0
4B	5	2	3	40.0	3	0	0.0
Total	26	10	16	38.5	15	1	6.3



Best in class efficacy:

- 83% of the patients who received the lead therapeutic dose reached complete healing.
- >30% wound size reduction in first 2 weeks treatment vs. >17% wound size increase in 2 weeks run-in period with SOC
- Median time to heal: 6.7 weeks / 65 days.
- No recurrence of healed wounds after 12 months follow-up.
- **No Dose Limiting Toxicity,** no systemic or local safety nor tolerability issues.

EXAMPLE: Cohort 2, low dose 2.5E+06 cfu/cm² 3 times per week for 6 weeks



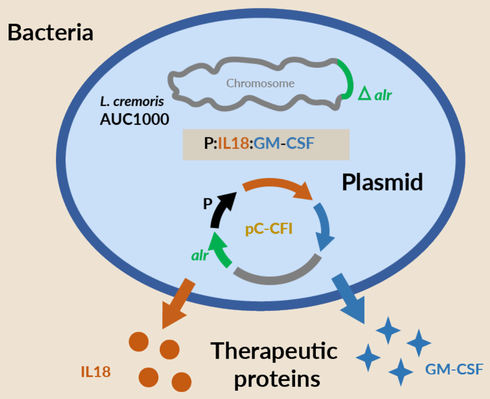
Before treatment Wound 10 weeks old | End of treatment 6 weeks | 2 weeks after end of treatment | 4 weeks after end of treatment

AUP-55 FOR ONCOLOGY

OVARIAN AND PERITONEAL CANCER

MODE OF ACTION

CONSTRUCT



Lactococcus cremoris AUC1000	Genetically engineered strain for food-grade plasmid selection
Δalr	Food-grade plasmid selection; host strain cannot grow without the plasmid
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IL18	Boosts cell-mediated immune responses and generates antitumor immune response via induction of IFNγ. Increases cytotoxicity and proliferation of T- and NK- cells.
GM-CSF	Vital factor in the development and maturation of antigen presenting cells. Directs the immune system towards the Th1-type response. Has shown clinical activity as an immune stimulant in tumor cell and dendritic cell vaccine studies.

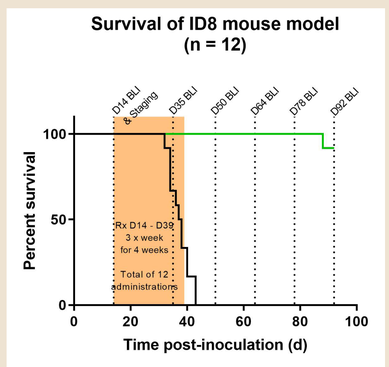
PRE-CLINICAL STUDY

AUP-55 enables complete survival in interperitoneal mouse ovarian cancer model ID8.

Model: interperitoneally implanted ID8-Luc-mCH-Puro. TD1 murine ovarian carcinoma model in female albino C57Bl/6 mice.

Treatment: AUP-55 = mIL18-mGM-CSF

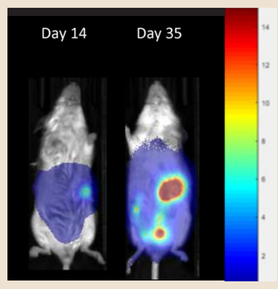
Group	N	Treatment	Dose	Application site	Days of treatment
1	12	5% dextrose, 0.9% NaCl	250 µl/injection	IP	14, 16, 18, 21, 23, 25, 28, 30, 32, 35, 37, 39
2	12	AUP5591m-C	1.0E+08 cfu/injection	IP	14, 16, 18, 21, 23, 25, 28, 30, 32, 35, 37, 39



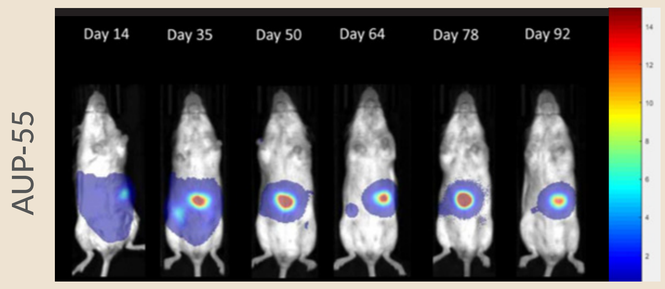
BLI = Bioluminescent Imaging

In the ID8 model, treatment was started 14 days after tumor implantation. Most untreated mice were terminated due to the disease progress. Treatment with AUP-55 resulted in 91.3 % survival and lower tumor load during the study duration of 81 days compared to the 0 % survival and massively increased tumor load in untreated mice.

All AUP-55 treatments were well tolerated. In the pathology post-mortem, all untreated animals had typical findings for ovarian cancer, such as ascites and high number of tumor nodules present in abdominal cavity, liver, spleen, kidney and pancreas. In the group treated with AUP-55 there were no macroscopic tumor deposits detected.



All vehicle treated mice died before Day 45.



Stable disease in AUP-55 and 100% survival (tumor exists but does not grow/kill). Treatment started on day 14 and ended on day 39.

CONCLUSIONS

Cytokine armed *Lactococcus cremoris* AUP-55 enables multimodal action. Treatment with AUP-55 suggests anti-tumor activity as a single therapeutic entity for the treatment of ovarian cancer and peritoneal carcinomatosis.

SUMMARY

The modular design of Aurealis' platform and gene therapy products makes them an ideal system to approach complex multi-factorial diseases such as chronic wounds and cancer. The proof of concept and positive Phase 1 clinical trial results by Aurealis helps to pave the way for a new generation of multi-factor gene therapies for unmet medical needs.