Infection Biology

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New strategies to combat bacterial and viral infections

Infectious diseases remain a leading cause of death worldwide. Modern procedures including complex surgeries, cancer treatment and transplantation are associated with high risk of infections. Emerging resistance of pathogens are serious threats increasingly limiting the effectiveness of the antimicrobials in use today. Our research group explores host- and pathogen-specific aspects of infectious diseases in a strong translational setting – with the overarching goal to identify new treatment strategies.

New treatment strategies for staphylococci

Health care associated/nosocomial infections – the fourth leading cause of disease in industrialized countries – are a major health issue. Together with Gram-negative microorganisms, Staphylococcus aureus is one of the major causative agents.

Staphylococcal strains are highly virulent and are increasingly becoming resistant to every clinically available antibiotic. One particularly important unmet medical need for anti-S. aureus therapies is to treat biofilm-associated infections. Novel approaches to combat staphylococcal biofilm infections are therefore urgently needed. Together with our collaborators from the Department of Biosystems Science and Engineering (D-BSSE, ETH Zürich) we demonstrated that engineered designer cells containing a synthetic genetic circuit expressing lysostaphin under the regulation of human Toll-like receptor (TLR) 2, TLR1, TLR6, and CD14 can effectively sense methicillin-resistant Staphylococcus aureus (MRSA) implant-associated infections by detection of blood reporter proteins and prevent as well as cure infections in our tissue cage infection mouse model. This novel mammalian cell-based anti-infective approach was superior to conventional antibiotics (Fig. 1/2). (www.cell.com/action /doSearch?searchType=quick&searchText=immunomimetic+cells&searchScope=fullSite& occurrences=all&code=cellsite&contentType=video&startPage=).

Translation to clinics

Adoptive transfer of pathogen-specific donor-derived T cells is to date the most promising and feasible immunotherapeutic strategy in transplant recipients restoring the lacking T-cell function. Its potential as prophylactic or therapeutic treatment for viral infections after transplantation has been demonstrated.

We have pioneered virus-specific T-cell therapies in Switzerland. In a phase I/II study, in which we assess the feasibility of directly isolated virus-specific T cells using the cytokine capture assay, we test their safety in patients with treatment-refractory adenovirus, cytomegalovirus or Epstein-Barr virus infections after allogeneic hematopoietic cell transplantation (Clin Trials ID NCTO2007356). Currently, ten patients of which five patients each received CMV or EBV virus- specific T cells have been included. We are currently working on an improved cell expansion protocol for clinical use (Fig. 2).

In December 2019, the University of Basel has received the grant to establish the National Center of Competence (NCCR) in Research “AntiResist”, directed by the Biozentrum. Together with researchers at the Biozentrum, and the D-BSSE we will establish a unique interdisciplinary center for the development of new strategies in the fight against antibiotic-resistant pathogens (https://nccr-antiresist.ch/).

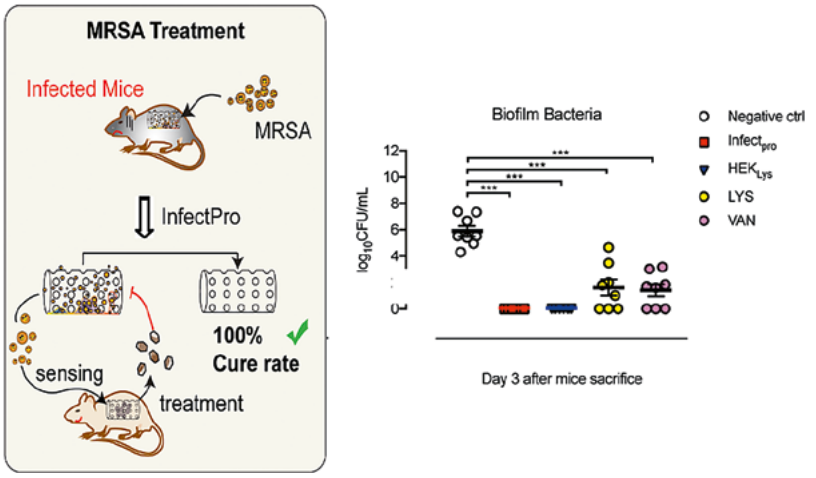

Fig. 1: Curing acute MRSA infection in Mice. To evaluate Infectpro's potential for the treatment of acute MRSA foreign-body infections, infected mice were treated with microencapsulated pYL25/pYL30/ pYL3-transgenic HEK293 cells (negative ctrl), HEKLys, Infectpro, recombinant lysostaphin (LYS, 5 mg/kg, once), or vancomycin (VAN, 200 mg/kg, every 12 hr). After 3 days, adherent MRSA in tissue cage biofilms of treated mice were evaluated.

Selected Publications

Wüthrich D, Cuénod A, Hinic V, Morgenstern M, Khanna N, Egli A, Kuehl R (2019). Genomic characterization of inpatient evolution of MRSA resistant to daptomycin, vancomycin and ceftaroline. J Antimicrob Chemother, 74(5):1452–1454.

Liu Y, Bai P, Woischnig AK, Charpin-El-Hamri G, Ye H, Folcher M, Xie M, Khanna N*, Fussenegger M* (2018). Immunomimetic designer cells protect mice from MRSA infection. Cell., 174(2):259–270.e11.

Woischnig AK, Gonçalves LM, Ferreira M, Kuehl R, Kikhney J, Moter A, Ribeiro IAC, Almeida AJ, Khanna N, Francisca Bettencourt A (2018). Acrylic microparticles increase daptomycin intracellular and *in vivo* anti-biofilm activity against Staphylococcus aureus. Int J Pharm., 550(1-2):372–379.

Schürmann N, Forrer P, Casse O, Li J, Felmy B, Burgener AV, Ehrenfeuchter N, Hardt WD, Recher M, Hess C, Tschan-Plessl A, Khanna N, Bumann D (2017). Myeloperoxidase targets oxidative host attacks to Salmonella and prevents collateral tissue damage. Nat Microbiol., 2:16268.

Stuehler C, Bernardini C, Elzi L, Stoeckle M, Zimmerli S, Furrer HJ, Gunthard H, Leibundgut- Landmann S, Battegay M and Khanna N (2016). Immune recovery in HIV-infected patients after Candida esophagitis is impaired despite long-term antiretroviral therapy. AIDS, 30(12):1923–33.

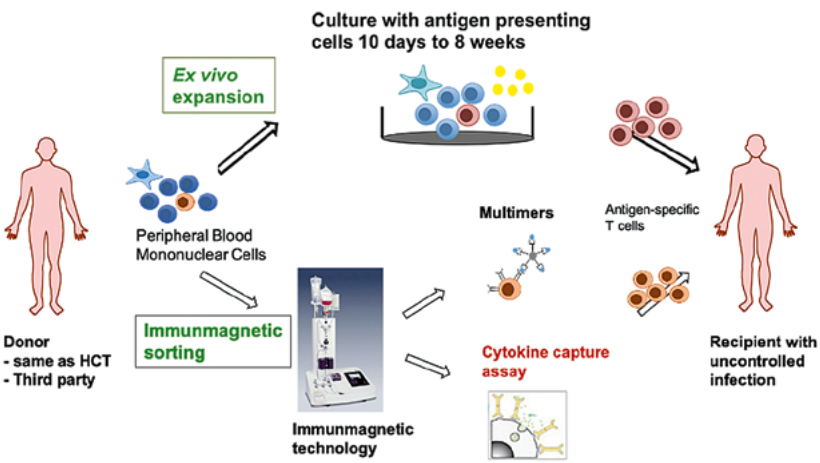

Fig. 2: Virus-specific T-cell therapies – current strategies. Virus-specific T cells for T-cell therapy (derived from the original stem cell donor or from a matched third party donor) can be obtained either by *ex vivo* expansion (top) or direct isolation via immunomagnetic sorting (bottom). For *ex vivo* expansion peripheral blood mononuclear cells are stimulated with antigen in the presence of cytokines for 10 days to several weeks to expand and enrich antigen-specific T cells. For immunomagnetic sorting antigen-specific T cells are directly isolated from peripheral blood by multimer technology or Cytokine capture assay (Miltenyi Biotech) within 1 to 2 days.