

Vaccination against cytokines to treat chronic inflammation

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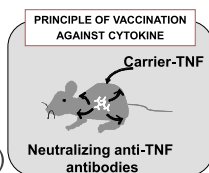
Context

Targeting cytokines is efficient for treating chronic inflammation, ie: anti-TNF in rheumatoid arthritis, Crohn's disease, psoriasis (2 000 000 people treated with TNF blocking agents). Improving such strategies is mandatory (inconstant achievement of remission, escapes, costs). Alternative strategy: active immunotherapy targeting cytokines:

- to obtain neutralizing anti-cytokine antibodies (ie: breaking tolerance)
- to maintain high safety conditions (cytokine blockade should be transient).

Development program

- Synthesis of vaccines: by coupling of a macromolecule to cytokines (or peptides of cytokines)
- Using relevant experimental models
- Clinical trials in selected patients
- Using vaccines as tools for pathophysiological studies of the diseases

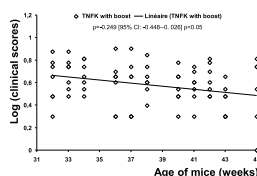
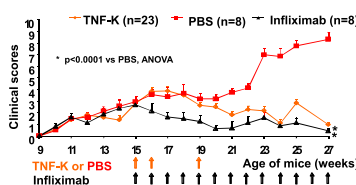


Vaccination with human TNF-K

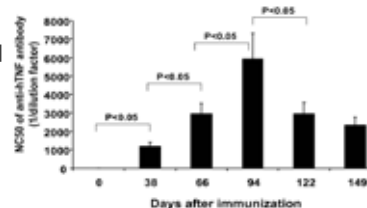
- Vaccine design: Human TNF- α was complexed to keyhole limpet hemocyanin (KLH) with glutaraldehyde to form hTNF α -KLH heterocomplex (TNF-K, NéoVacs, Paris).
- Effect of TNF-K in acute inflammatory model:
 - Prevention of TNF-dependent lethal shock conferred by sera from TNF-K immunized mice (1).
- Effect in a murine model of arthritis: the human TNF transgenic mice (TTG):
 - TNF-K is effective in protecting TTG mice in early treatment (2).



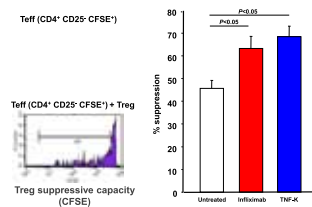
➢ TNF-K is effective in treating chronic established arthritis and flares in TTG mice (3).



➢ TNF-K vaccination induces a bell-shaped curve neutralizing Ab response (3).



➢ TNF-K vaccination and infliximab both arm T regulatory cells to inhibit effector T cells (4).



• Clinical trial (phase II) in human rheumatoid arthritis and Crohn's disease: in progress (promotor: NéoVacs, Paris)

Other developments

- Murine TNF-K (entire cytokine and peptides of TNF)
- Vaccines against other cytokines:
 - VEGF-K (cytokine and peptides)
 - IL-23-K (peptides)

Conclusion

- Translational studies resulting in a clinical trial on a novel strategy of targeted biotherapy in chronic inflammation.
- Preclinical safety studies are positive.

Main publications

1. Le Buanec H, Delavallée L, Bessis N, Paturance S, Bizzini B, Gallo R, Zagury D, Boissier MC. TNFalpha kinoid vaccination-induced neutralizing antibodies to TNFalpha protect mice from autologous TNFalpha-driven chronic and acute inflammation. Proc Natl Acad Sci U S A. 2006;103(51):19442-7.
2. Delavallée L, Le Buanec H, Bessis N, Assier E, Denys A, Bizzini B, Zagury D, Boissier MC. Early and long-lasting protection from arthritis in tumour necrosis factor alpha (TNFalpha) transgenic mice vaccinated against TNFalpha. Ann Rheum Dis. 2008;67(9):1332-8.
3. Delavallée L, Semerano L, Assier E, Vogel G, Vuagniaux G, Laborie M, Zagury D, Bessis N, Boissier MC. Active immunization to tumor necrosis factor-alpha is effective in treating chronic established inflammatory disease: a long-term study in a transgenic model of arthritis. Arthritis Res Ther. 2009;11(6):R195.
4. Bion J, Semerano L, Delavallée L, Lemeiter D, Laborie M, Grouard-Vogel G, Boissier MC, Bessis N. Interplay between TNF and regulatory T cells in a TNF-driven murine model of arthritis. J Immunol. 2011;186(7):3899-910.

Main collaborators of the project

P. Decker, L. Delavallée, A. Denys, E. Duvallet, G. Falgarone, G. Grouard-Vogel, D. Lemeiter, L. Semerano, R. Ratsimandresy, G. Vuagniaux, D. Zagury. 14 international centers (clinical trials)

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