INSTITUT PASTEUR — UNIVERSITE PIERRE & MARIE CURIE

The 2nd PSU International Teaching Platform on Tumour Immunology and Immunotherapy

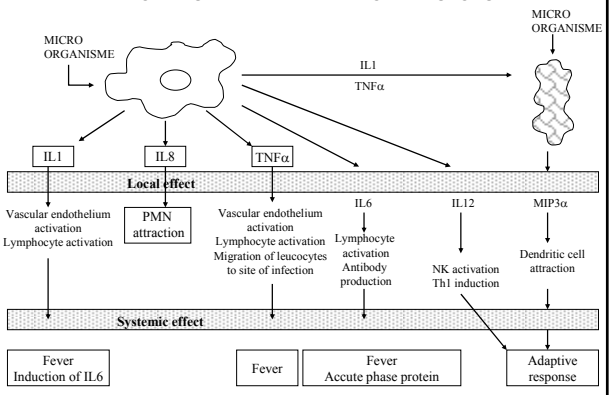
Jointly organized by
Prince of Songkla University, Université Pierre et Marie Curie (Paris 6) and Institut Pasteur

December 15 – 20, 2003
At The Department of Biomedical Sciences
Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla, Thailand

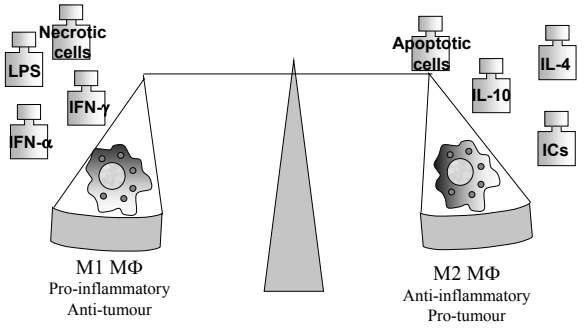
Lecture 5:
Non-specific cellular therapy
Prof. Hervé Fridman

December 16, 2003

CYTOKINES IN THE INFLAMMATORY RESPONSE



Macrophage delicate function balance



Macrophage anti-tumour effector functions

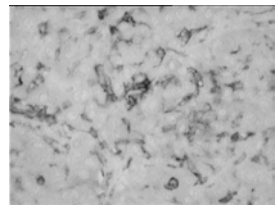
- Phagocytosis: CR3, FcR
- ADCC: FcR (CD16, CD64)
- Soluble secreted factors: cytokines: TNFα, IL1β
- Soluble secreted factors: metabolites and other molecules: RONs, RNIs, prostaglandins, proteases
- Receptor mediated: Fas-FasL apoptosis induction

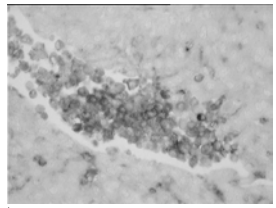
Macrophage pro-tumour effector functions

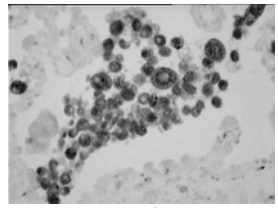
- Phagocytosis: apoptotic cells or via IC
- Soluble secreted factors: cytokines: TGFβ, PDGF
- Soluble secreted factors: prostaglandins, Metalloproteases, RONs
- Receptor mediated: Inhibitory Fc receptor cross linkage, scavenger receptors

Characterization of interstitial DC and macrophages

CD14 / CD68





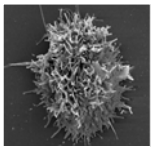


Cell Drugs against cancer

Blood

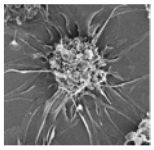
GM-CSF + IFN-γ

GM-CSF + IL-13



Macrophages

MAK CELL PROCESSOR



Dendritophage™

VACCELL Processor

Phase I/II clinical trial of intravesical administration of MAK ™ in patients with superficial bladder cancer

- Rationale of this immunotherapeutic approach:
  - widespread use of adjuvant BCG-therapy.
  - local immunostimulation with an increasing number of macrophages and CD4 T cells.
  - Th1 associated cytokines (IFN-γ, IL-2, IL-12, IL-18) detected in urine of BCG-responders.
  - *in vitro* and murine models: IFN-γ activated macrophages are able to kill tumor cells.

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Design of the clinical trial

IDM Immuno-Designed Molecules

- Study design :

17 patients with TaGIII or rec.TaGII superficial bladder cancer

TUR → TaGII/III → 1 month → apheresis (10.10^9 mononuclear cell-enriched leukocytes) → *MAK™ preparation:* GM-CSF: 500 UI/ml J1-J6, IFN-γ: 250 U/ML J7, $2x10^8$ MAK™ / bag

- Therapeutic schedule:

Aph.	D7	D14	D21	D28	D35	D42	M3	M6	M9
	MAK n°1	MAK n°2	MAK n°3	MAK n°4	MAK n°5	MAK n°6	MAK n°7	MAK n°8	MAK n°9

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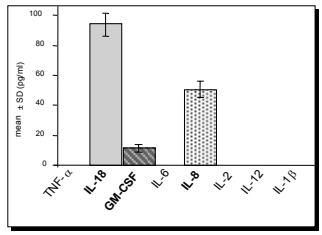
Cytokine production by MAK™ *in vitro* when incubated in urine



(Pagès F. et al, Clin. Exp. Immunol. 2002)

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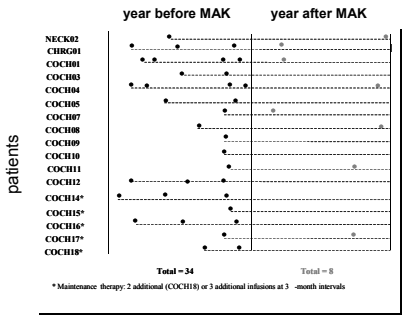
Clinical outcome



sign rank test: p = 0.0005

(Thiounn N. et al, J. Urol. In press)

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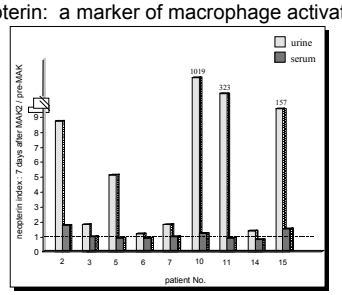
Neopterin in urine and blood samples

- neopterin: a marker of macrophage activation



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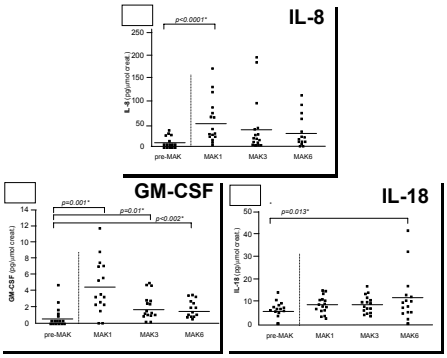
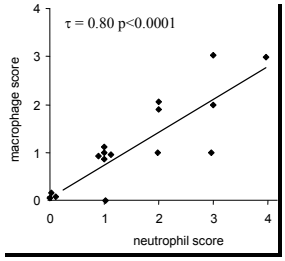
Cytokines in urine 2 hours after MAK infusions



Cytological evaluation of urine 2 months after treatment



Conclusion

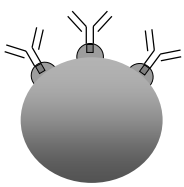
- Infusion of IFN-γ activated macrophages in the bladder results in IL-8, IL-18 and GM-CSF production in urine.
- This argues for a local immunostimulation and is associated with a decrease of local tumour recurrences.
- Macrophages in an activation state persist weeks after infusions.

Safety

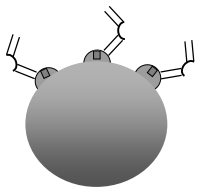
- Administration of MAK™ or DF™ is very well tolerated regardless of the route of injection.
- Out of 605 cell injections carried out by IDM in 89 patients in 5 clinical studies, no serious events related to treatment were reported.
- Only minor events (grade I or II) were observed in a limited number of patients.

Antibody-based Cell Drugs

MAK armed with conventional mAb



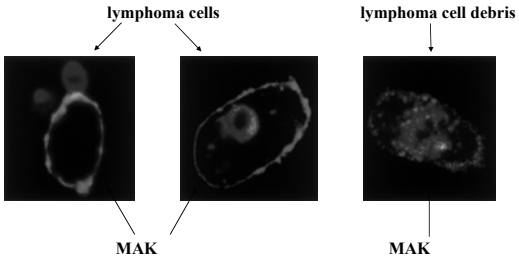
MAK armed with bAb



FDA-APPROVED INNOVATIVE DRUGS

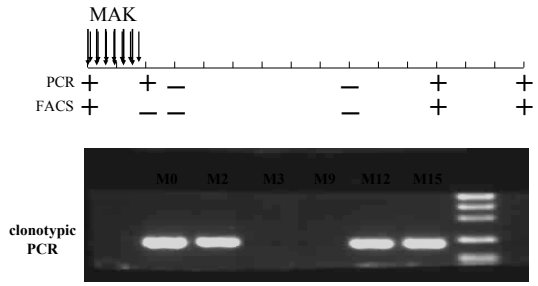
NAME	CLASS	INDICATION
GLIVEC	Antityrosine Kinase	CML
HERCEPTIN (Her2/neu)	Monoclonal antibody	Breast cancer
RITUXIMAB (CD20)	Monoclonal antibody	Lymphomas
CAMPATH (CD52)	Monoclonal antibody	CLL

Monocyte-derived Activated Killer cells



Fadul et al.

Transient elimination of tumour cells in a CLL patient



MAK + @CD20 in CLL. Principal Investigator : L. Sutton

MAK-based clinical trials

	I/II (IDM)	17	De Gramont *et al., Genycol. Oncol.,* 2002
	III (IDM)	60	on going
	I/II (IDM)	17	Thiounn *et al., J. Urol,* 2002
	II (Monnet)	19	Monnet *el al., Chest*, 2002
	I/II (Sutton)		on going
	I/II (Favrot)		on going
	I/II (Wallace)		on going
	I/II (Prince)		on going

Autologous cell-based therapy