Scientific Barriers to Investigation of Novel Combinations

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- Tumor Models :
- Differences with human - Not predictive?
  - Bill Murphy
- Clinical trials - Difficulties:
  - Mike Lotze
- Important predictor(s) for objective response?
  - Monitor IR in patients receiving combination therapy.. What? How? When?

Preclinical Tumor models to Predict Effective combinations

Dose

Schedule

Sequence

Prioritizing combinations

Threshold

Drug Interactions

Scientific Barriers: Preclinical Tumor models

- Most models do not reflect long-term tumor-bearing state.. 6mo – yr..
- Established - how long..
  - Is size enough?
  - Time tumor “on board”.
  - Transplantable tumors grow too fast - suppression / not sufficient time to induce sufficient IR.
- Transgenic animal model(s) should have..
  - Inflamatory component, inducible --

Predictors: Autoimmunity

- Vitiliego : Human and mouse
- What else to evaluate in preclinical models?
  - Autoantibodies predict better outcome to IFN.
  - Other.. What?
  - Collaborate with autoimmunity researchers?

Caveats when using mouse preclinical cancer models

1. Species differences (mouse versus man)
    a. pharmacokinetics/drug sensitivity
    b. immune biology
    c. life span

2. Mouse issues
    a. strain used
    b. housing conditions (SPF)
    c. age

3. Tumor model
    a. cell line immunogenicity
    b. growth kinetics
    c. routes of administration/orthotopic

	Mouse	Human
Hematopoiesis in spleen	Active into adulthood	Ends before birth
Presence of BALT	Significant	Largely absent in healthy tissue
Neutrophils in periph. blood	10-25%	50-70%
Lymphocytes in periph. blood	75-90%	30-50%
Leukocyte defensins	Expressed on granulocytes	Expressed on monocytes
CD4 on macrophages	Absent	Present
Predominant T cells in skin and mucosa	γ/δ TCR (dendritic epidermal T cells – DETC)	α/β TCR
NK inhibitory Rs for MHCI	Ly49 family (except Ly49 and H)	KIR
NKG2D ligands	H-60, Rae1β	MIC A, MIC B, ULBP

Mestas and Hughes. 2004. Of mice and Not Men: Differences between Mouse and Human Immunology. *JI*. 172:2731-2738.

	Mouse	Human
Effects of γ_c deficiency	Loss T, NK, B cells	Loss T, NK, but normal B cell numbers
IFN-α promotes Th1 differentiation	No	Yes
Th expression of IL-10	Th2	Th1 and Th2
CD28 expression on T cells	On 100% of $CD4^+$ and $CD8^+$	On 80% $CD4^+$, 50% $CD8^+$
ICOS deficiency	Normal B cell numbers and function, normal IgM levels	B cells immature and severely reduced in number, low IgM
B7-H3 effects on T cells	Inhibits activation	Promotes activation
MUC1 on T cells	Absent	Present

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	Mouse	Human
IL-8, NAP-2, ITAC, MCP-4, HCC-1, HCC-2, MPIF-1, PARC, eotaxin-2/3	Absent	Present
IFN-γ effects in demyelinating disease	Protective in EAE	Exacerbates MS
Constitutive MHCII on EC	Absent	Present
T cell dependence on CD2-ligand interactions	Low	High
CD40 on EC	Absent	Present

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- Clinical trials - Difficulties: Mike Lotze
  - Having testable hypotheses with solid answer at the end
  - including: suitable biomarkers; problems of accessing the tumor site;
  - endpoints of tumor destruction/death - LDH, HMGB1, S100 molecules, HSPs

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- What are properties of effector T cells that mediate tumor regression.. TCR affinity, Peforin - other, homing molecules
- What are factors that prevent T cells from working
- What are tumor factors that prevent tumor from being destroyed