IMMUNE THERAPIES FOR CANCER: BIMODALITY - THE BLIND SPOT TO CLINICAL EFFICACY – LOST IN TRANSLATION

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Abstract

Multiple attempts at improving the clinical success rates of cancer therapies, including immunotherapies, show *variable, confusing results, with few complete responses*, the remainder being PR, SD and progressive disease.

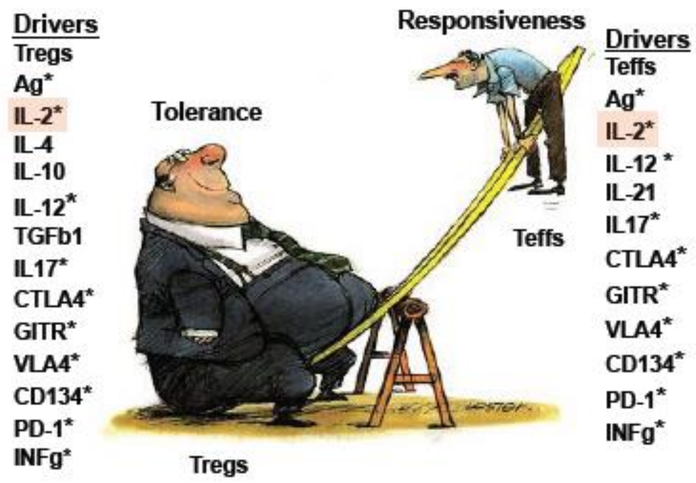
It is widely assumed that observed response heterogeneity - a feature almost independent of therapy type (cytotoxic chemotherapy, radiation, biological, pathway blocker, antibody, or vaccine) - is due to resistant cancer cell clones, antigenic variations and/or poor antigen presentation. Lack of research progress suggests antigenic variability, defective tumor antigen presentation, and even cytotoxic resistance are probably not main causes.

T-cell immune responses can be detected in most, if not all, cancers indicating *on-going underlying pre-exisiting endogenous immune response occurs in most cancer patients*, but is rendered ineffective by 'skewing' the immune response balance towards a regulatory, rather than effector, dominance. Recent literature strongly implicates predominant T-regulatory response as the most likely culprit for in-vivo immune response clinical ineffectiveness, in most tumor types.

Emerging evidence shows *many cytokine receptors are transiently bimodally expressed on both effector and regulatory cells*, rather than on one cell type alone, as previously thought. The net effect of cytokines, acting through the specific receptor (eg. IL2/IL2R) is determined by numbers of receptors expressed on a particular cell type at the time of exposure to the cytokine. Moreover, the relative predominance of cytokine receptor expression - either on effector or regulatory cells - would be expected to determine the direction the immune response is driven (responsiveness or tolerance) at the time of therapy.

The time of administration of the agent (cytokine, vaccine, CTLA4 inhibitor, antibody or even cytotoxic) *appears critical* to determine the intensity, direction and clinical efficacy of the respective therapeutic agent.
It would explain the heterogeneous mix of complete and partial responses and failure to respond, and how repeat therapies sometimes produce successful clinical results, where they did not initially. Repeated frequent therapies, and combined chemo-immuno therapies could be explained using this reasoning. Pre-conditioning therapies might optimize the probability of successful therapeutic immune responses. All of these are predicated upon the most optimal timing of therapies to engineer more effective clinical responses. Reported *immune system cyclical behaviour & Bimodality would explain the paradoxical observations* with most therapies and the lack of progress to date.

Homeostatic Regulated Immune Kinetics in Cancer



Many cytokines & receptors are bimodal, - proinflammatory and immunoregulatory.

"Nature exists in a delicate balance, the immune system being no exception."

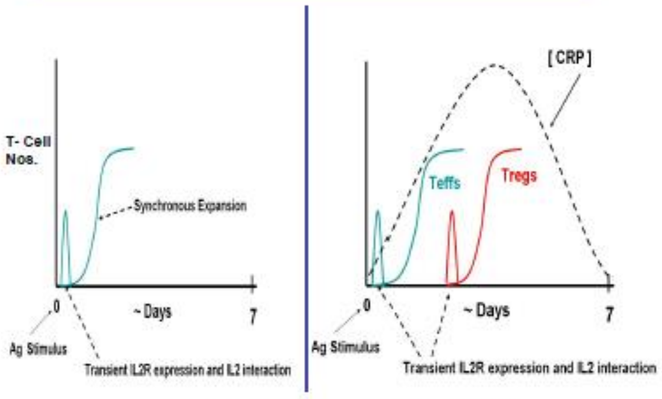
IL2 : The first identified Bimodal Cytokine

- Proinflammatory (initially) & Immune Regulatory (recently).
- Needed for Both Responsiveness and Tolerance
- Needed for Teff & Treg clonal expansion and maintenance
- Longest history of clinical use in cancer Immunotherapy (1992 to present in advanced Melanoma and Renal Ca)
- Manipulating an existing anti-cancer Immune Response
- Delivers a fixed Complete Response Rate of ~7%...Reason?

IL2 – IL2R Immune Kinetics

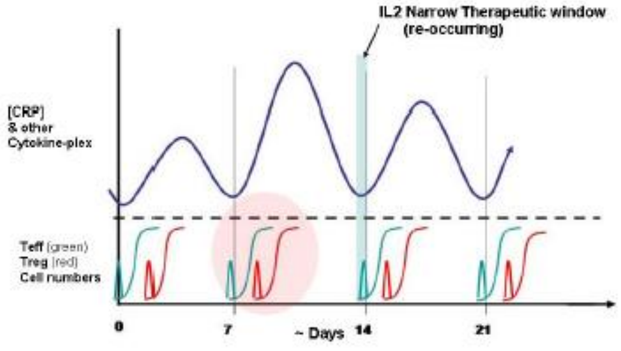
- Short IL-2 Half-Life (5-15 mins)
- IL-2R briefly expressed (6-8 hrs)
- Transient Cytokine / Receptor interaction
- Both Teff & Treg require IL2 sequentially
- IL2 both Initiates and Terminates the Immune Response

IL2 / IL2R and the Immune Response



* These characteristics are all documented

IL2 Immune Regulation Kinetics - a Cyclical Phenomenon



Our Observations re the Cyclical Immune Response

Bimodal, Sequential & Transient IL2 Cytokine / Receptor interaction on Teffs then Tregs within a constant repeating Cyclical Immune Response… Implications …..

- Predicts narrow, reoccurring therapeutic windows. …. ~12 hrs every ~7 days
- Therapeutic windows can be accidentally "hit" with the Random application of IL2 leading to a mean ~7% therapeutic barrier
- Hypothesis can be tested by examining the clinical trial literature since 1992

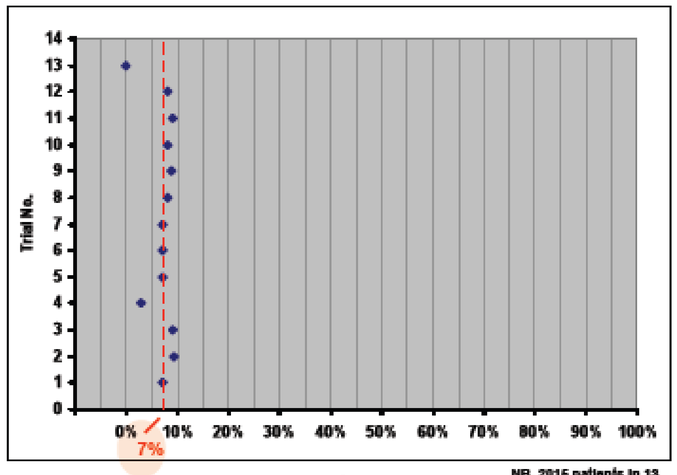
Clinical Trials with IL2 in Metastatic Melanoma and Renal Ca *

Patients Number	Disease	Dose	Endpoint	Reference
283	melanoma/RCC	high 720,000 IU/kg	7% CR, 15% PR	Rasenberg [74]
409	melanoma/RCC	high 720,000 IU/kg	8.3% CR	Rasenberg [75]
281	RCC	high 720,000 IU/kg	9% CR, 10% PR	Lindsey [76]
325	RCC	high 720,000 IU/kg vs low IV 72,000 IU/kg	3% vs 7% CR, 17% vs 8% PR	Yang [79]
386	RCC	high 720,000 IU/kg vs low IV 72,000 IU/kg	7% vs 4% CR, 14% vs 8% PR	Yang [80]
192	RCC	high 600,000 IU/kg vs low SC $5x10^6$IU/m^2 +IFN-α	23.2 vs 8.9% RR	McDermott [81]
255	RCC	high 600,000 -720,000 IU/kg	7% CR, 8% PR	Fisher [82]
259	RCC	high dose 720,000 IU/kg	8.9% CR, 11.6% PR	Klapper [83]
212	RCC	high	8% CR, 12% PR	Belldegrun [84]
157	RCC	IL-2 + IFN-α	9% CR, 21% PR	Belldegrun [84]
26	RCC	low SC $9-18x10^6$ IU	8% CR, 15% PR	Sleijfer [77]
41	RCC	low SC $9x10^6$ IU	0% CR, 17.1% PR	Sheng [78]

CR: complete response, PR: partial response, RR: response rate.

* Grivas P & Redman B et al.
Current Clinical Pharmacology, 2011, 6, 151-163

CR Rates with IL2 in Metastatic Melanoma and Renal Ca *



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NB. 2016 patients in 13 trials/ trial arms:
Av CR Rate = 6.7%

Prediction

Complete Response Rates may be substantially increased via Timed "Immune Synchronized" IL2 administration

Potential Immediate Clinical & Economic Benefits

- Improved CR Rates / Efficacy
- Reduced Toxicity
- Reduced Cost
- Wider Pan-Cancer Applications [Beyond Melanoma & Renal Ca]