
Opportunities and Obstacles to Developing Novel Biologic Combinations: Academic Perspective

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Opportunities and Obstacles

- ◆ State of immunotherapy
- ◆ Opportunities for moving forward
- ◆ Obstacles
- ◆ Combination therapy issues
- ◆ Possible solutions

Quarter Century of Clinical Investigations with Biologic Agents

FDA approved immunotherapeutic agents

- Interferon
 - CML, HCL (not immunotherapy, no longer used)
 - Adjuvant melanoma (controversial)
- HD IL-2
 - only active in melanoma and RCC
 - No established survival advantage

High Dose IL-2 Therapy

1986



2006

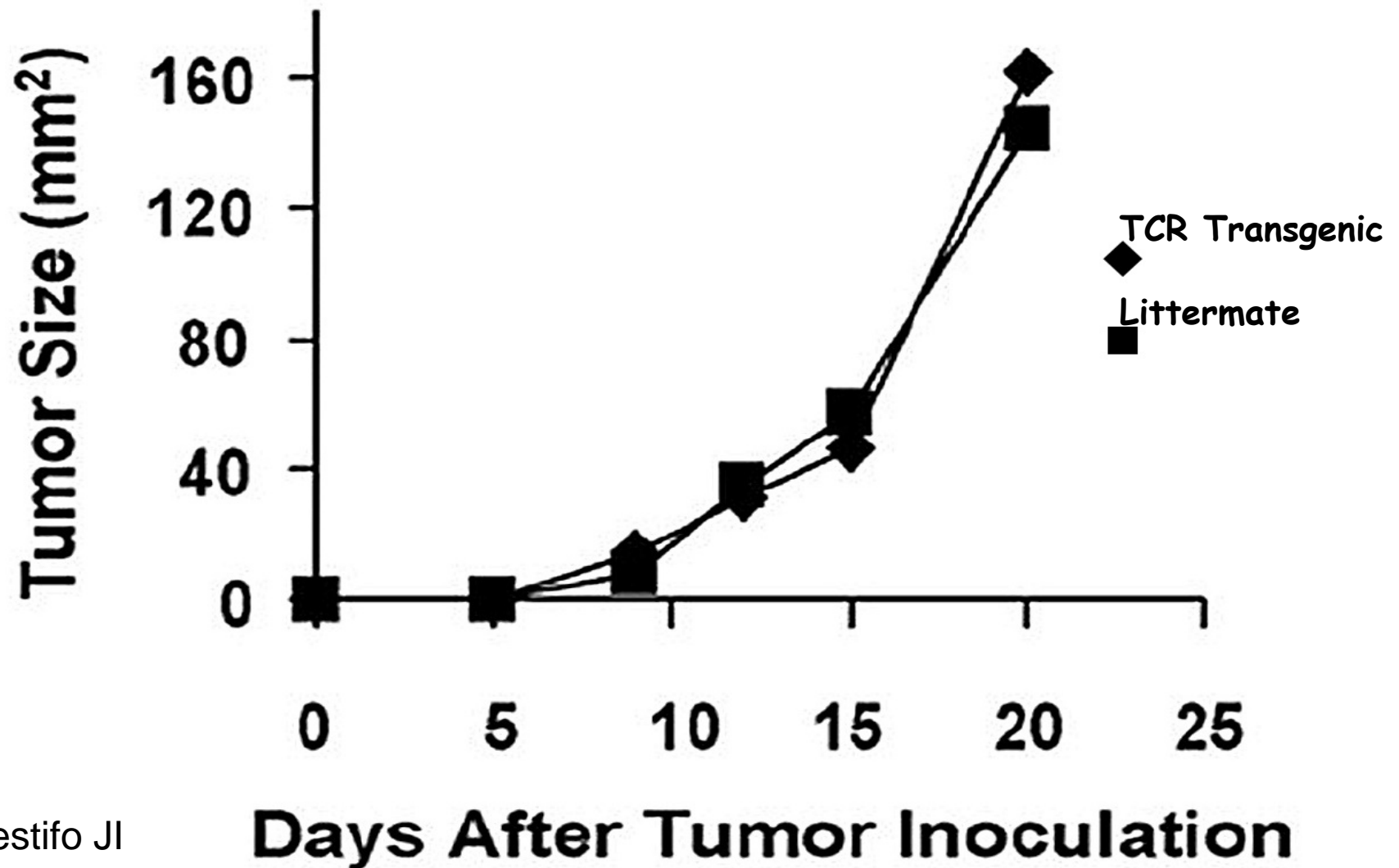
A case study for what is wrong with cancer clinical development

- ◆ Uncontrolled
- ◆ No target
- ◆ No target population
- ◆ Toxic
- ◆ Inpatient
- ◆ No correlates

Vaccine Therapy

- ◆ Hundreds of cancer vaccines tested
- ◆ Vaccine efficacy at anecdotal levels
 - Response rate = 2.6% (NCI SB)
- ◆ 2006 - no approved cancer treatment vaccines

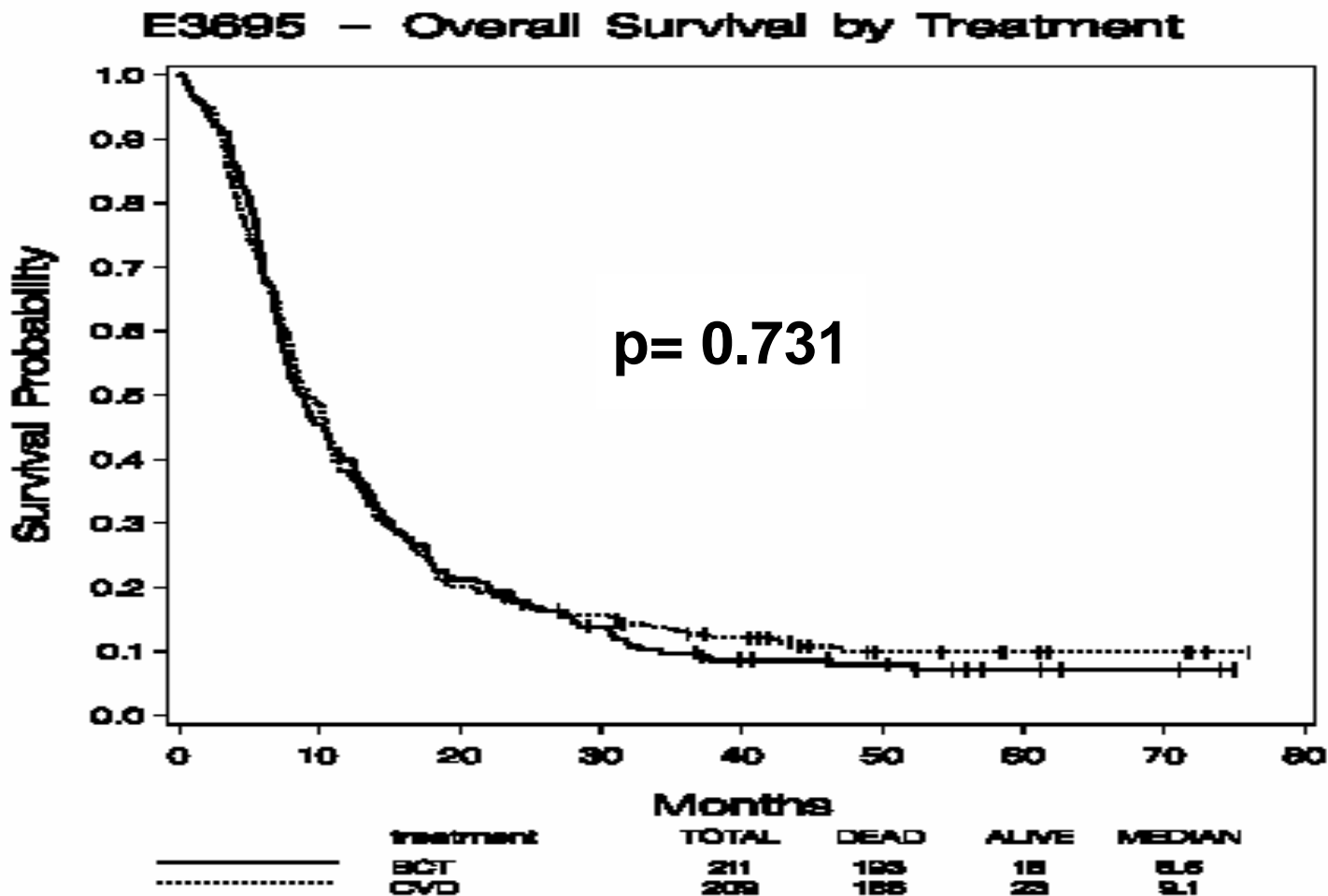
Tumor-Reactive T-Cells are Not Enough: Growth of Transplanted B16 Tumor in Mice With a Transgenic T-Cell Receptor for gp100



Biochemotherapy: "A Case Study"

- ◆ Phase II studies and meta-analyses suggested an advantage for cisplatin / IL-2-based biochemotherapy over chemotherapy or IL-2 alone
 - 50% response rates
 - 10-20% CR, 10% durable CR
- ◆ A single institution Phase III trial confirmed benefit of BCT over chemotherapy alone
- ◆ Phase III trials were initiated through the Cooperative Group mechanism

E3695: BCT vs CVD – 2005 update



Biologic Therapy-2006



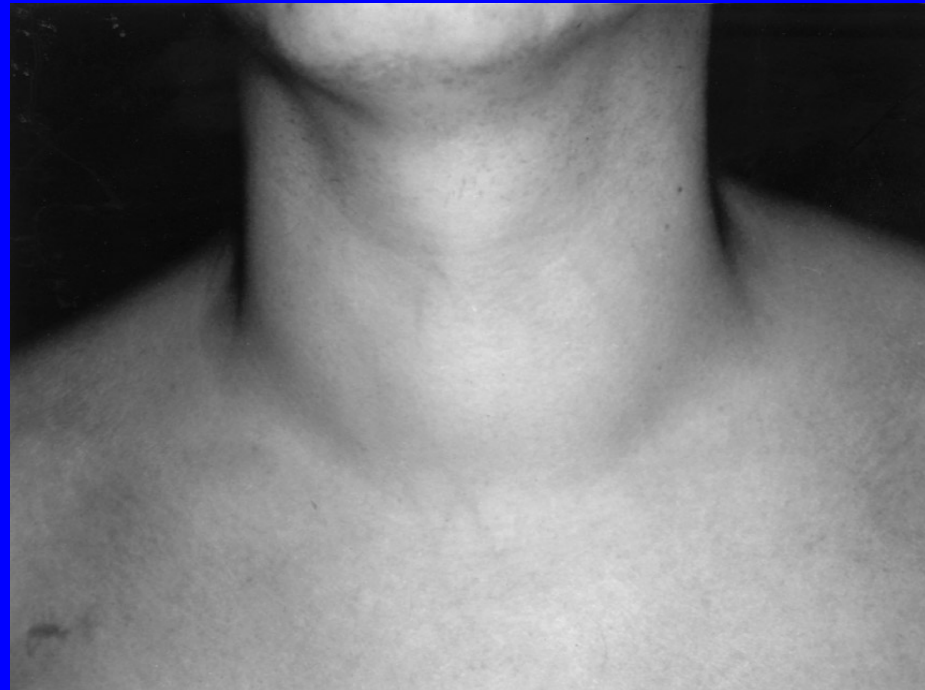
Which way to go from here?



Immunotherapy Opportunities

- ◆ Improved patient selection
 - Auto-immune pre-disposition
 - Immune responsive tumor phenotype/ profile
- ◆ Elimination of immune suppression / regulation
 - Lymphodepletion
 - Ontak
 - CTLA4 Ab
 - PD-1L / B7H1 inhibition
 - Regional immunotherapy

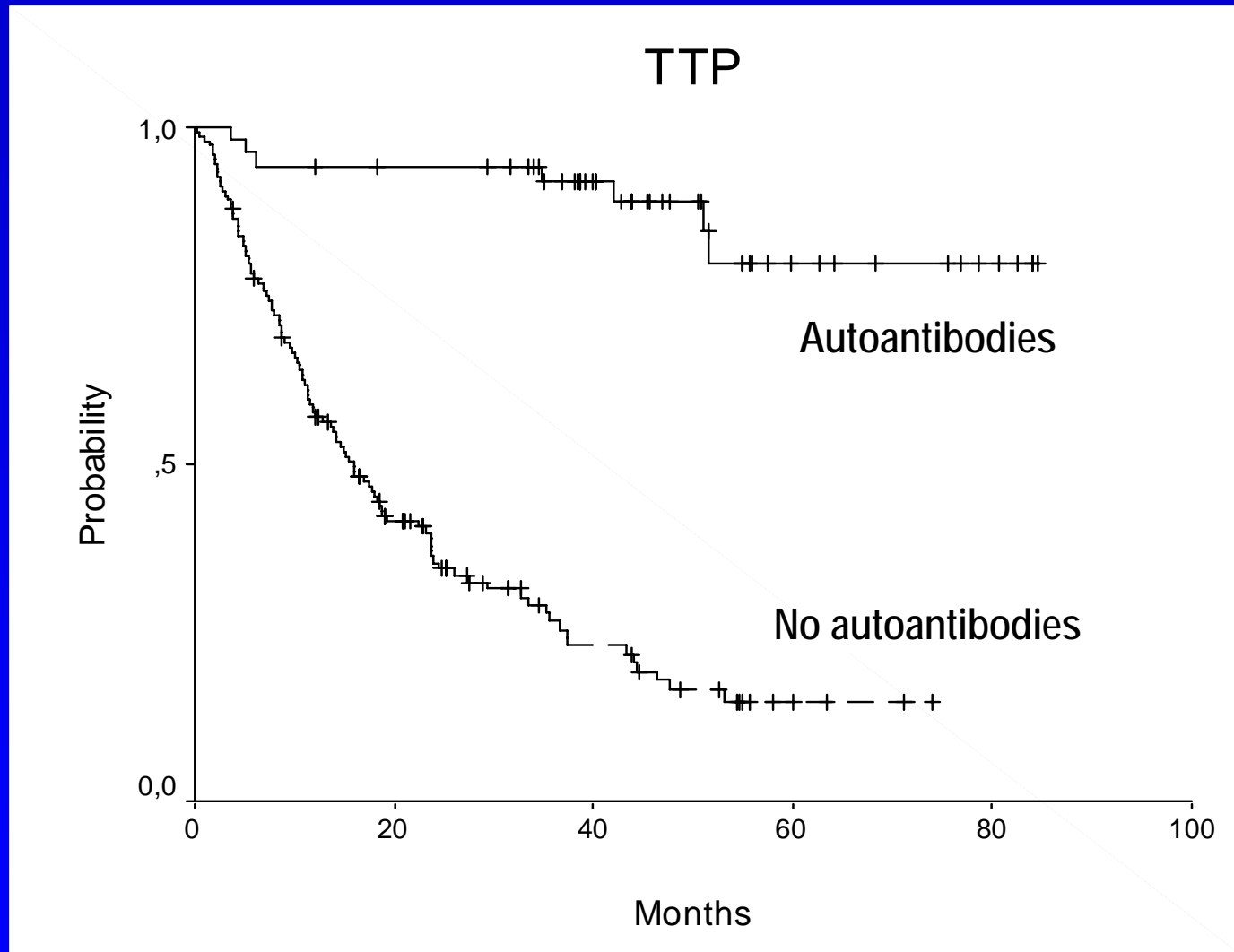
Vitiligo and hypothyroidism following HD IL-2 Rx



Treated May 1986 – Alive today without disease

Atkins et al NEJM, 1988

Time to Progression by auto-antibody status in melanoma patients receiving adjuvant IFN



CTLA4 Ab: Disrupts peripheral immune tolerance leading to autoimmunity and anti-tumor activity

Dose	Immune-related adverse events	
	Dermatitis	Diarrhea
10 mg (N=20)	2	10
15 mg (N=10)	0	2

Immune-related adverse events		Anti-tumor Response	No anti-tumor Response
Yes	12	4*	8
No	18	1	17

* $\chi^2 = 4.0$; $p = 0.0455$

Reuben et al-ASCO-2005

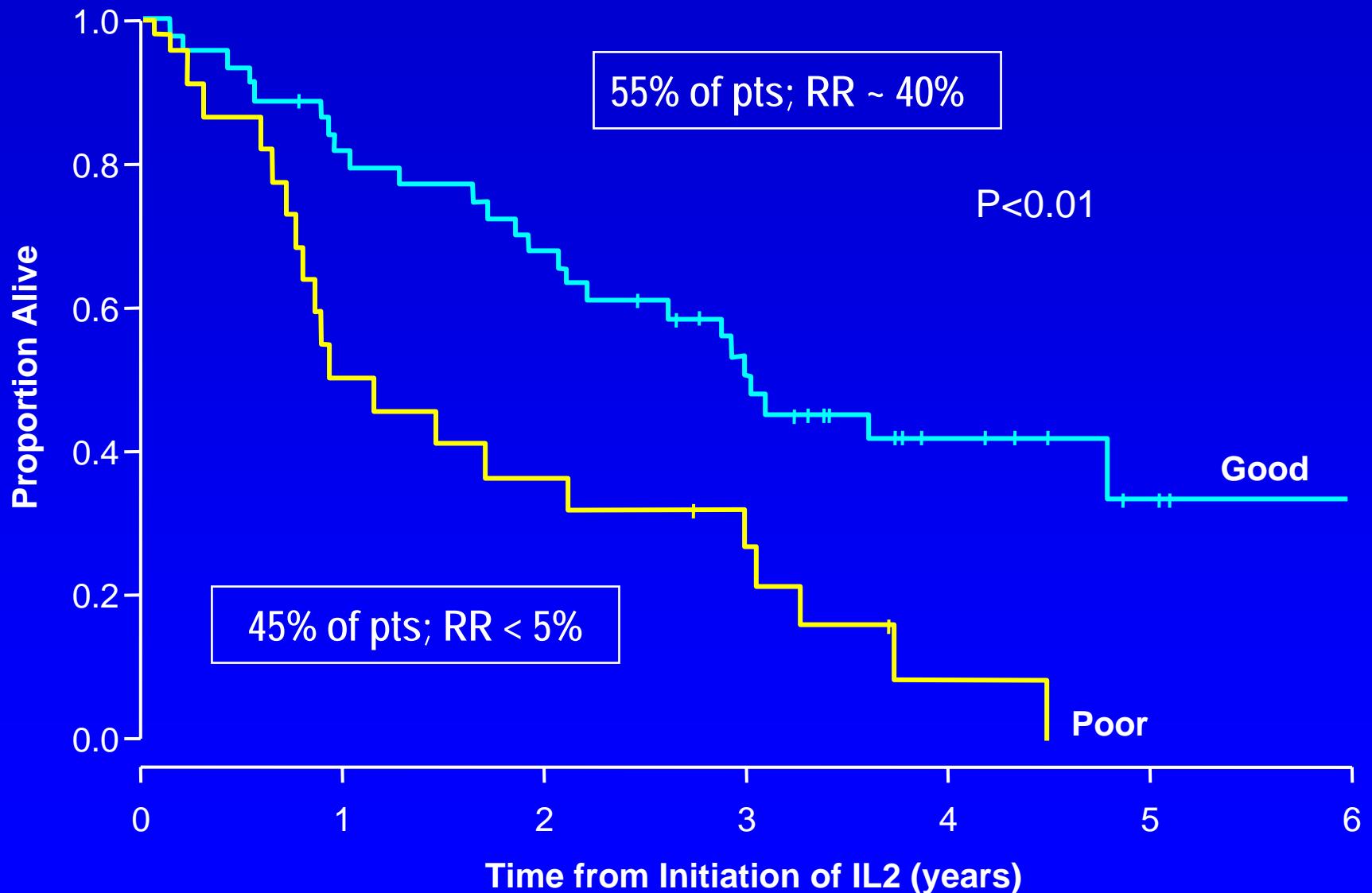
Immunotherapy and Autoimmunity: Implications

- ◆ Association of response with propensity to autoimmunity indicates that host genetic factors likely play a role in response to immune therapy
- ◆ We should be able to identify patients with a propensity to autoimmunity prior to treatment
 - Autoantibodies
 - HLA type
 - Treg / T effector balance
 - CTLA4 polymorphisms (Type 1 DM)
- ◆ What is the effect of the tumor?
 - Not all patients with autoimmunity respond
 - Autoimmunity develops in patients with other cancers that don't respond to immunotherapy
 - Vitiligo more frequent in patients with melanoma

Renal Cancer: IL-2 Selection Model

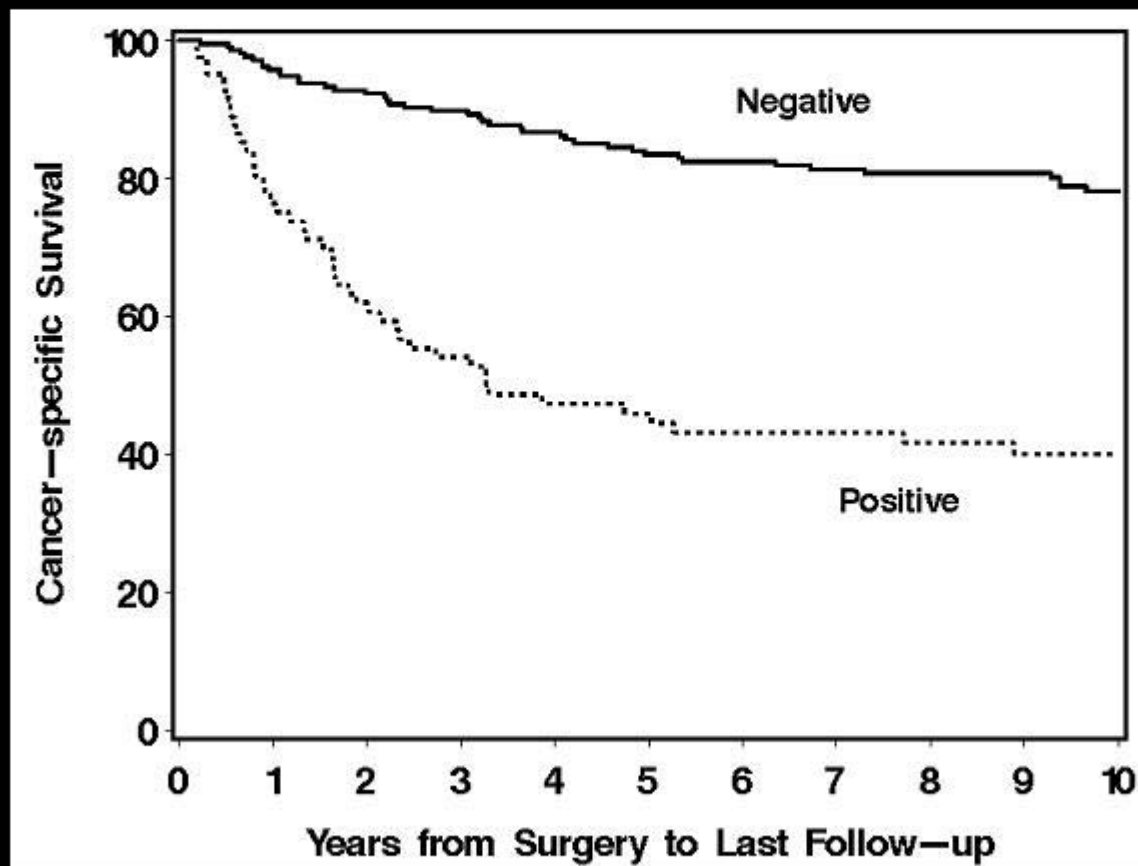
Refined Pathology Risk Group		Non-Responder (n=39)	Responder (n=27)
Good risk path or intermediate path with high CAIX	Good	18 (46%)	26 (96%)
Poor risk path or intermediate path with low CAIX	Poor	21 (54%)	1 (4%)

RCC: IL-2 Related Survival: Path and CAIX Model



Increased B7-H1 Expression in RCC Diminishes Survival

Tumor B7-H1

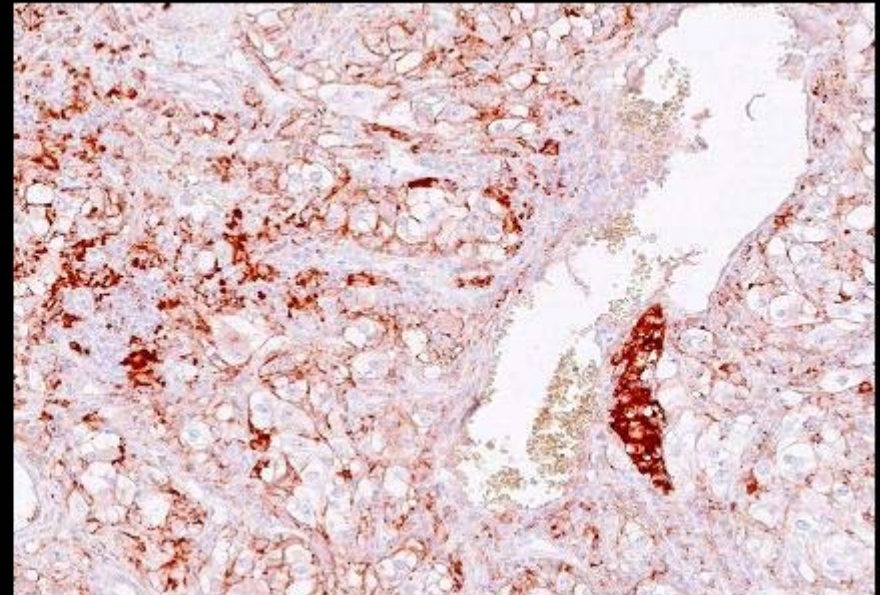
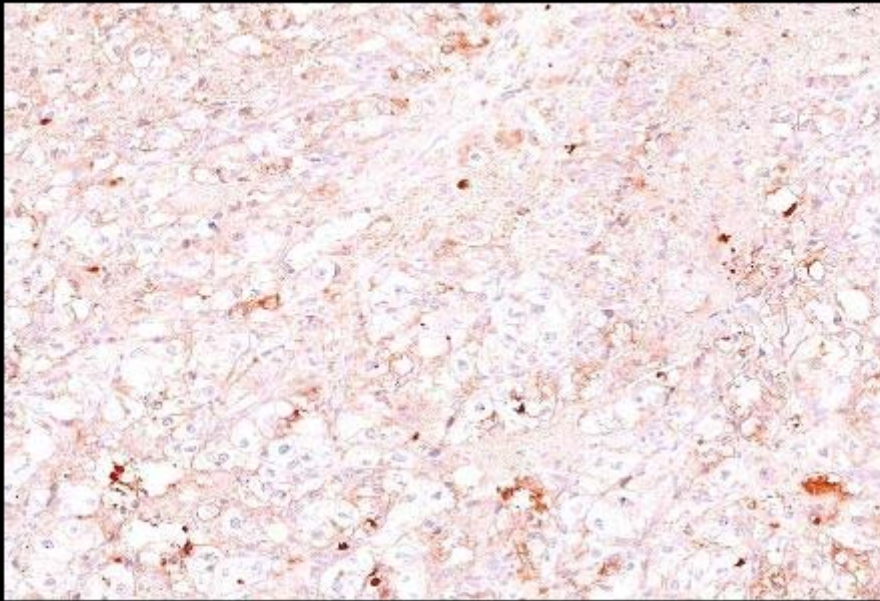


N = 306
Patients

Thompson,
Kwon
et al

Years from nephrectomy to last follow-up

Staining of IL-2 Patient TMA with B7H1 antibody



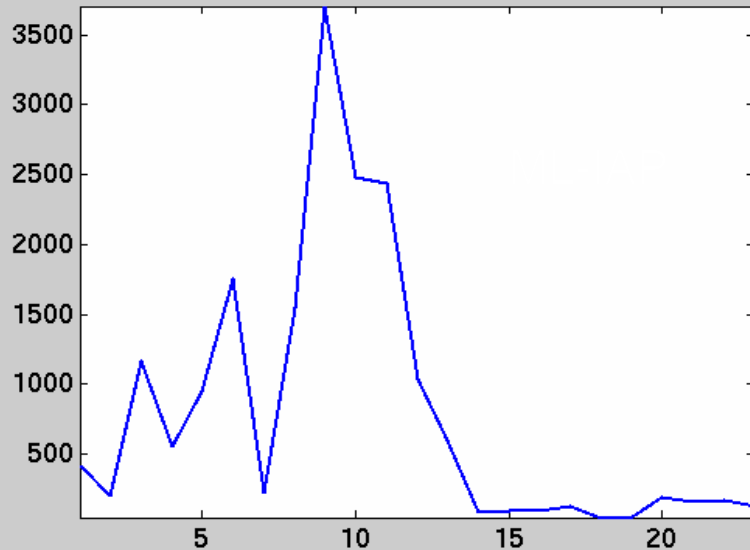
Lack of B7H1 expression yields two-fold increase in response to HD-IL-2

Courtesy of E. Kwon, Mayo Clinic

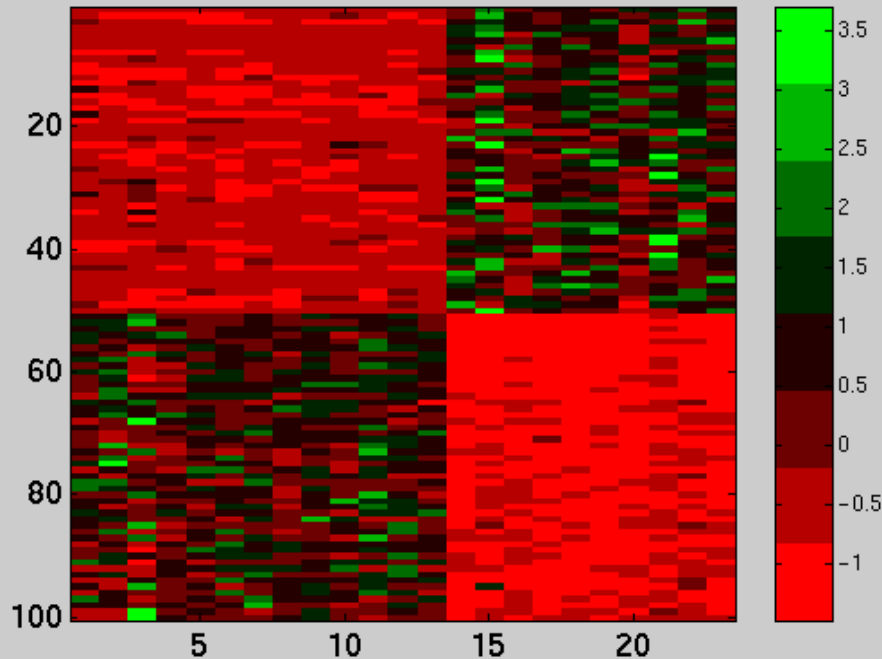
Todd Golub
Tom Flotte, Stefan Wagner
DFHCC Melanoma Program

Type 1 defined by MITF and
melanocyte Ag expression

ML-IAP, GP100, Tyrosinase, MelanA



Type 2 defined by “Immune” genes



C1

C2

Annexin A1
IL6R
Oncostatin M
MCSF
GMCSF
IL1 β
IL8
IL4R
Cathepsin S
CD83
Monocyte chemoattractant protein
IL5
IL12A
HLA Class II DM β

Relation Between G-Vac Induced "Response" and Melanoma subtype

Melanoma Class	N	Immune Response	Response Rate	P-value
Type 1	8	6	75%	P =0.01
Type 2	15	3	20%	

Patient Selection Opportunities for immunotherapy: Conclusions

- ◆ Selection opportunities exist for patients with cancer
- ◆ Immunotherapy continues to have a role in some cancers; it will likely remain an essential component of any curative treatment strategy
- ◆ Additional efforts to identify and enrich for patients with tumors more likely to respond to therapy are critical
 - **IHC staining and expression profiling of tumors from patients receiving immunotherapy**
 - **Assessment of immune function, HLA type and polymorphisms**
 - **Collection of autoantibody data**
 - **Working with autoimmunity field**
 - **Pooling of resources**

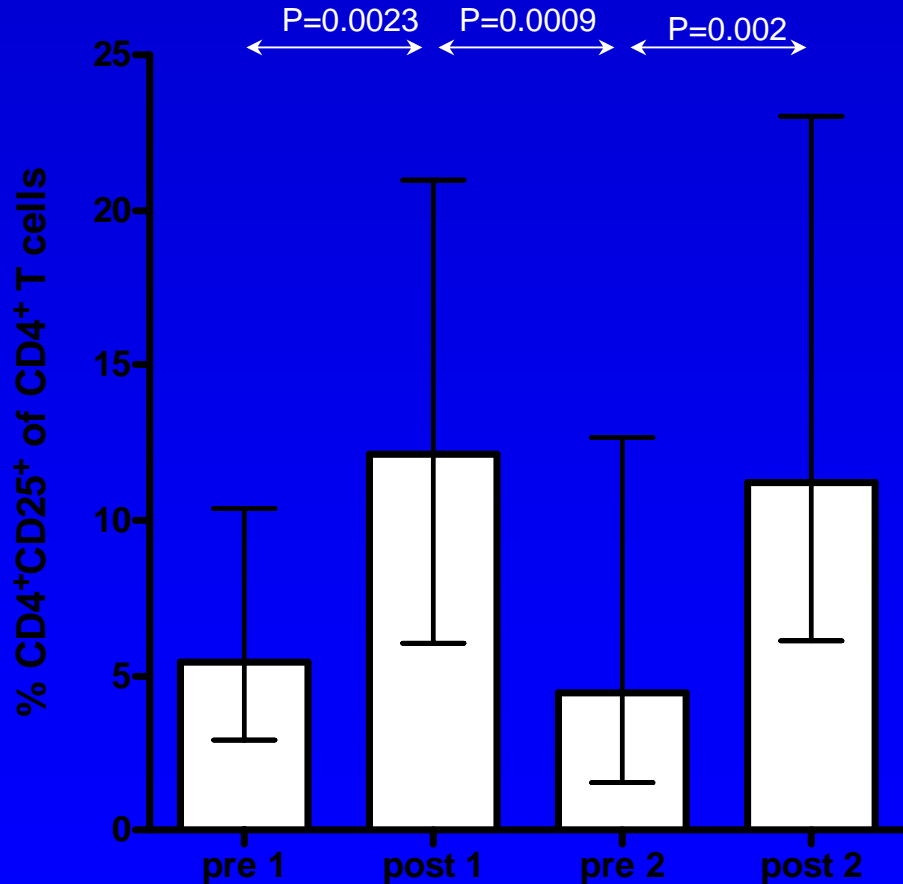
Overcoming Immune Suppression

Mechanisms of Immune Suppression

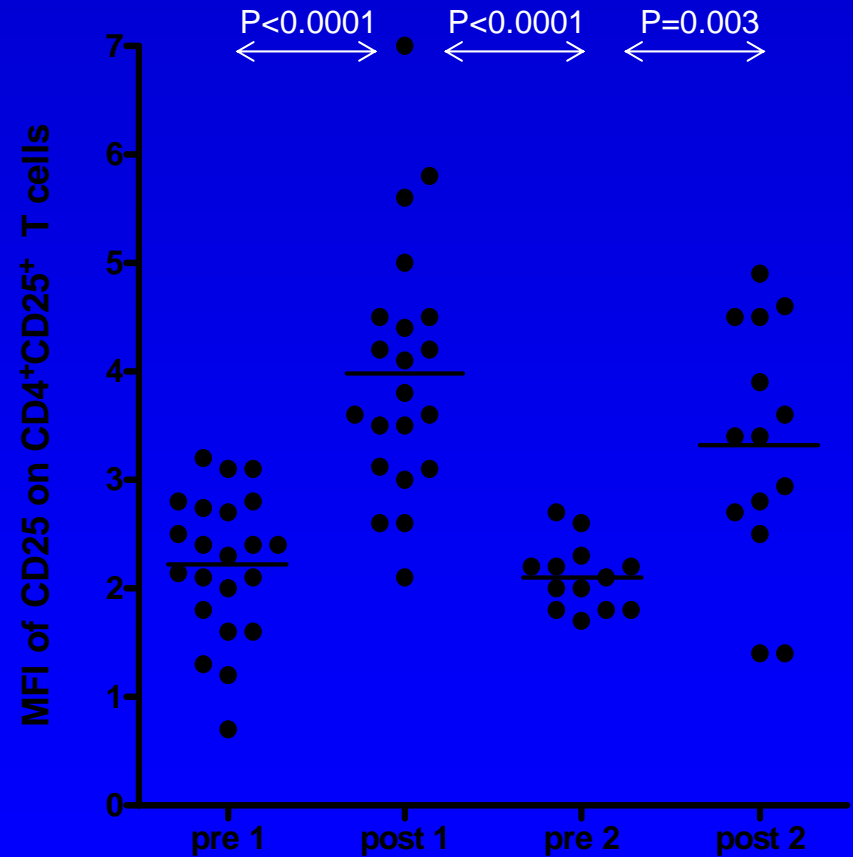
- ◆ Suppressor T cells- CD4/C25+ T regs
- ◆ Immune inhibitory molecules - B7H1,4 etc
- ◆ Cytokines - IL-10, IL-6 etc
- ◆ Micro-vesicle release
- ◆ Amino acid depletion
 - Arginase \longleftrightarrow diminished arginine
 - Indolamine Dioxygenase (IDO) \longleftrightarrow diminished tryptophan

High-dose IL-2: CD4⁺CD25⁺ T cells

Frequency



CD25 level



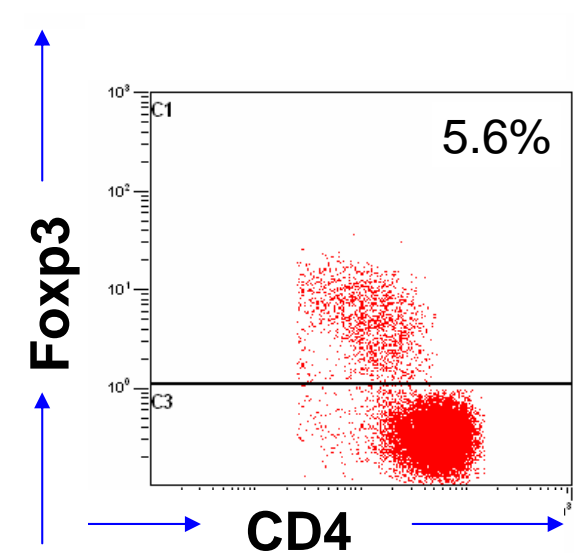
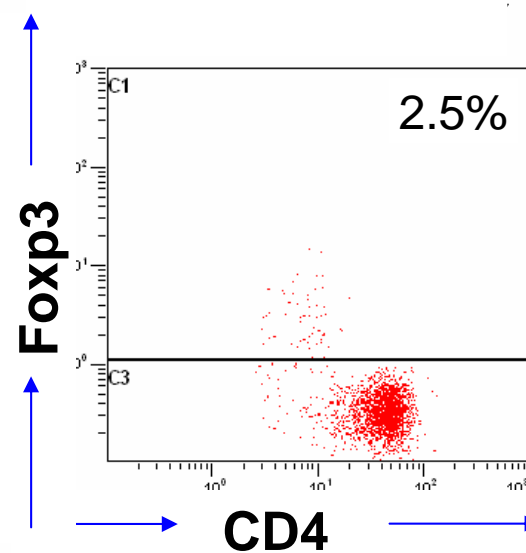
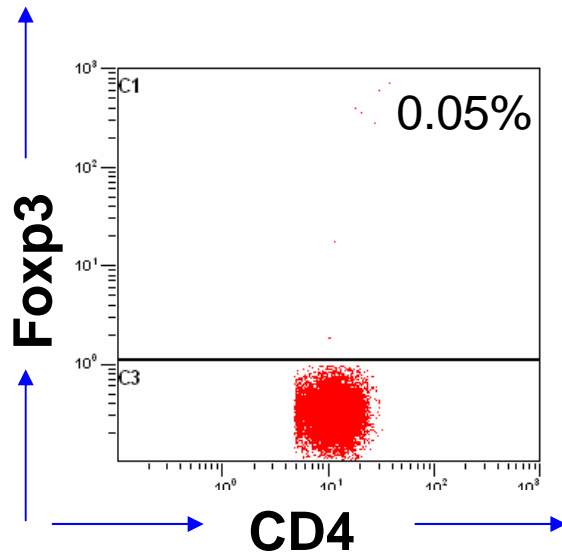
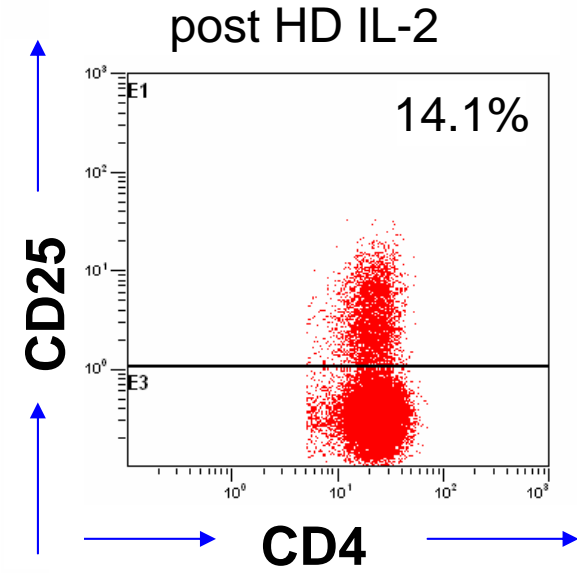
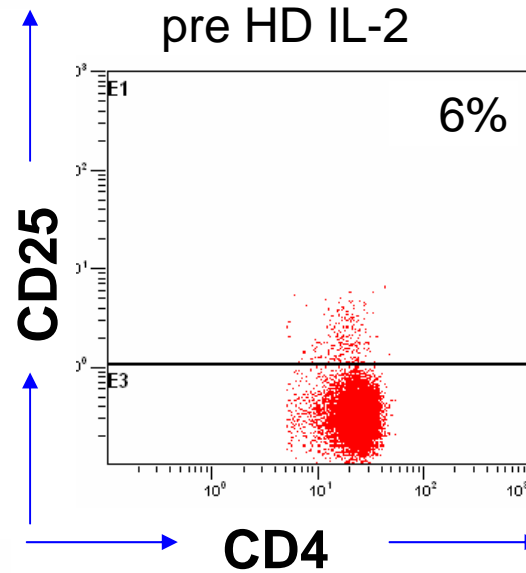
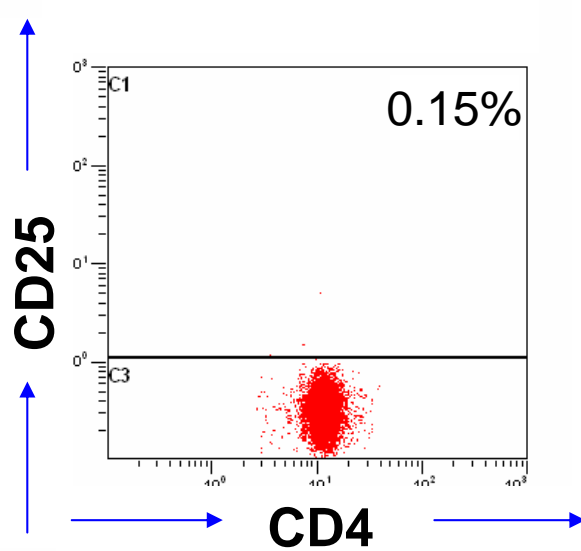
-significant increase in frequency and MFI of CD25 during 1st and 2nd cycle of HD IL-2



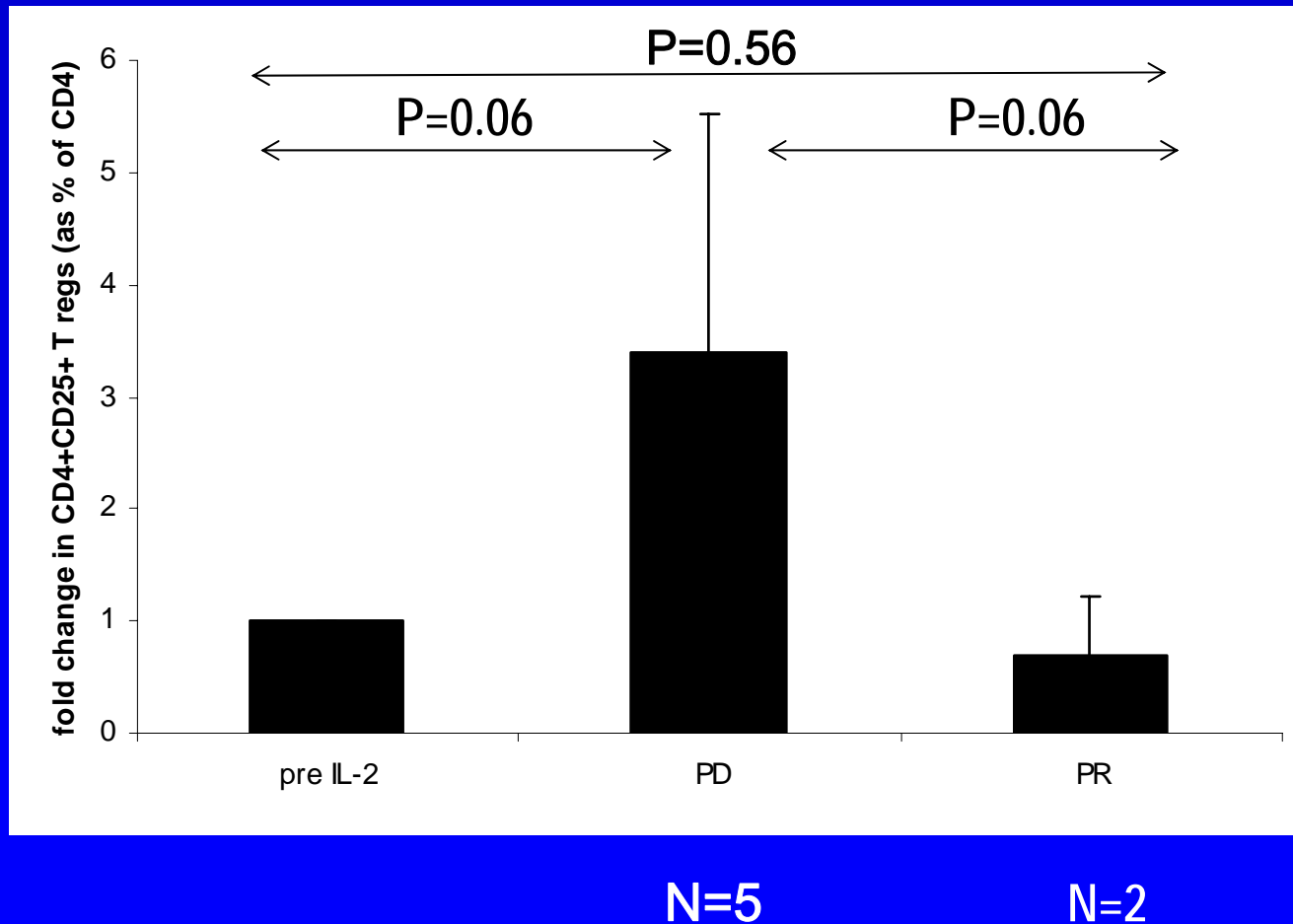
HD IL-2: Increases both CD4⁺CD25⁺ and CD4⁺Foxp3⁺ T cells

health

cancer



No increase in CD4⁺CD25⁺ regulatory like T cells in patients responding to HD IL-2



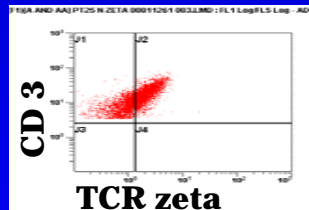
Alternative Means of Decreasing Tregs

We need a better way than lymphodepletion to eliminate Tregs prior to immunotherapy

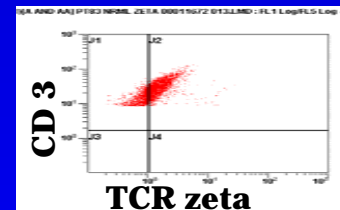
- ◆ Ontak (Johannes Viewig)
- ◆ Celebrex (Steve Dubinett)
- ◆ TLR agonists
- ◆ Other (? An antibody)

Tumor Induced Immune Suppression: Preliminary Data

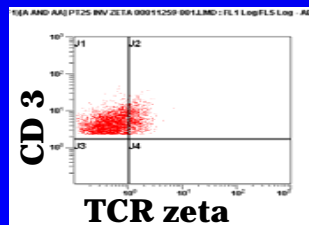
Preliminary flow cytometry data demonstrated decreased TCR ζ expression in tumor involved lymph nodes



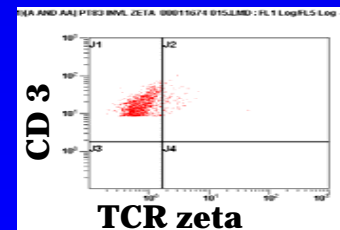
Patient 1
Non-Involved LN



Patient 2
Non-Involved LN

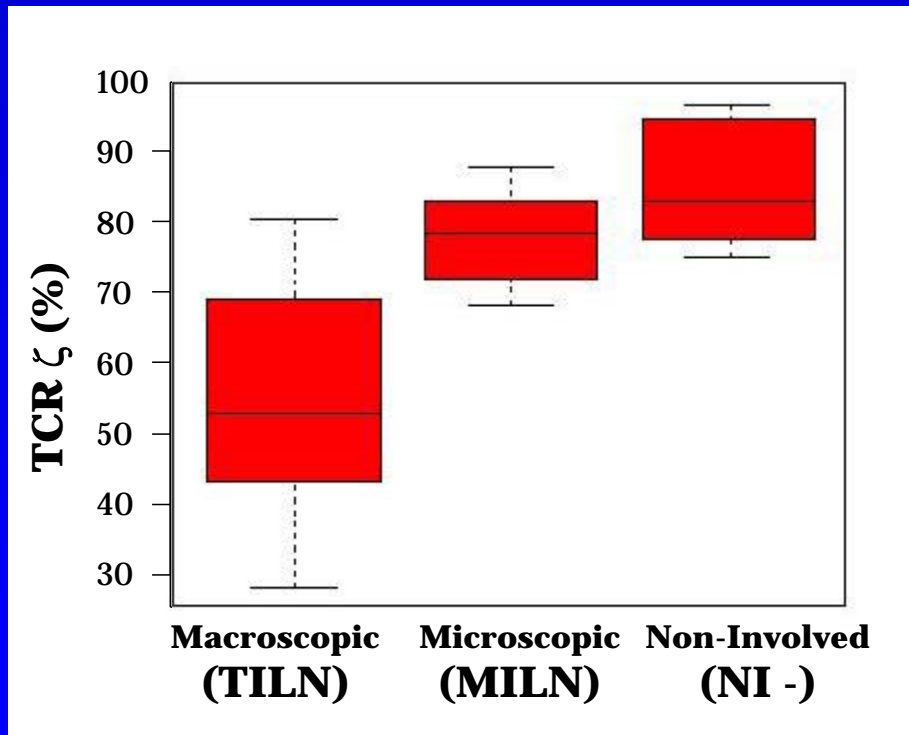


Patient 1
Involved LN



Patient 2
Involved LN

Immune Suppression Relates with Tumor Involvement



T Cell Receptor ζ (mean)

Non Involved: 85%

Microscopic: 76%

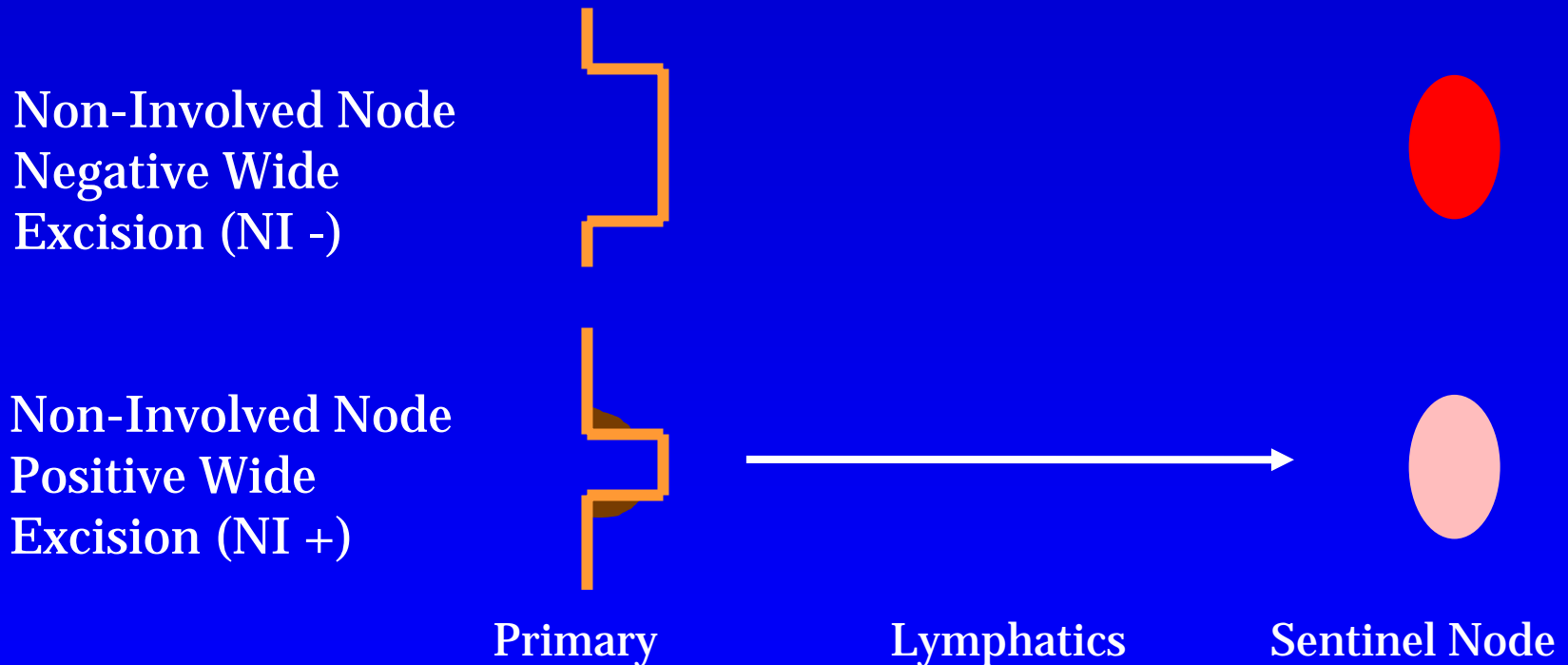
Macroscopic: 56%

Non-Involved vs. Macroscopic
($p < 0.0001$)

Microscopic vs. Macroscopic
($p = 0.001$)

Non-Involved vs. Microscopic
($p = 0.15$)

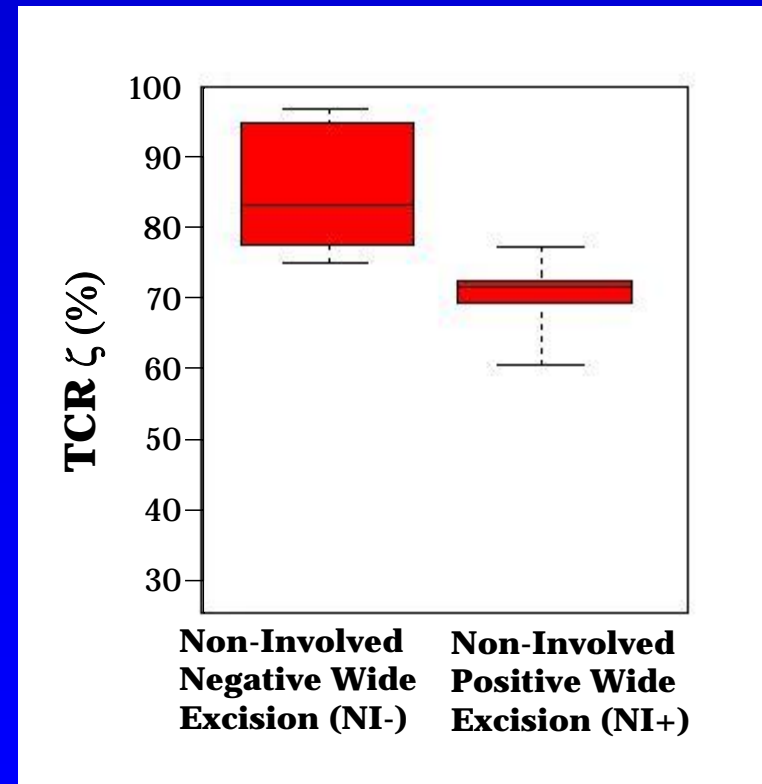
Immune Suppression Precedes Tumor Spread



Incisional or shave biopsy (remaining tumor continues to suppress)

Immune Suppression Precedes Tumor Spread

- ◆ Nodes downstream from a positive wide excision had significantly lower TCR ζ expression than those with no tumor upstream. (70% vs. 85%; $p = 0.034$)
- ◆ All non-involved nodes were negative for tumor by histology and MART-1 PCR.



Regional Immune suppression: Conclusions

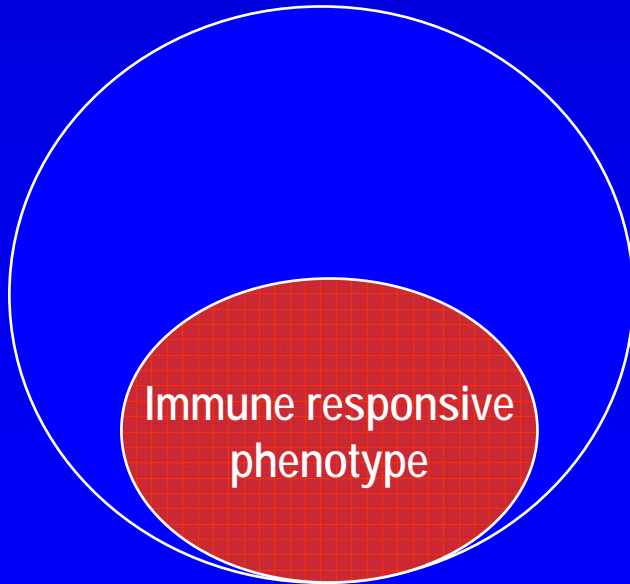
- ◆ The presence of tumor in a lymph node is significantly correlated to immune suppression as represented by decreased expression of the TCR ζ subunit
- ◆ The degree of immune suppression by melanoma increases significantly with increasing tumor burden
- ◆ The presence of remaining primary tumor after an incisional biopsy is significantly associated with TCR ζ loss in the draining SLN
- ◆ This creates a potential new paradigm that also enables unique clinical trial designs

Overcoming Tumor Induced Immune Suppression- Conclusions

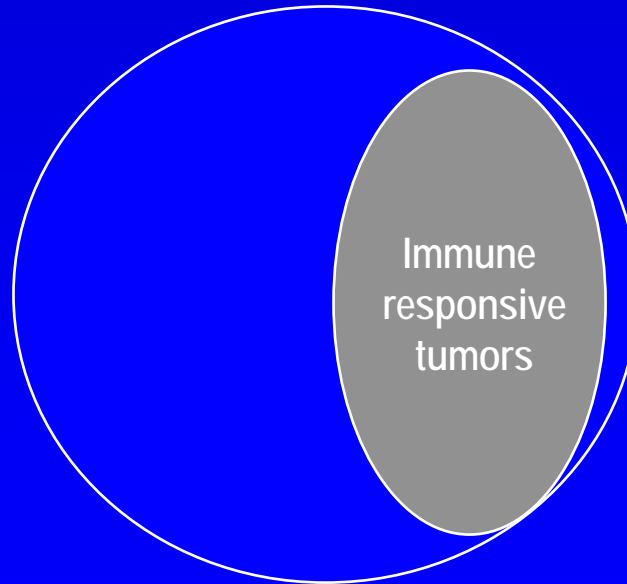
- ◆ Immunotherapy appears to enhance tumor-induced immune suppression in many cancer pts
- ◆ Opportunities exist for inhibiting tumor-induced immune suppression
 - Lymphodepletion
 - ? ONTAK and others
 - B7H1-PD-1L Ab therapy
 - IDO blockade- 1 methyl tryptophan
 - Earlier therapy
 - Stage IV NED
 - Adjuvant therapy
 - “Regional immunotherapy”

Immunotherapy Selection Model

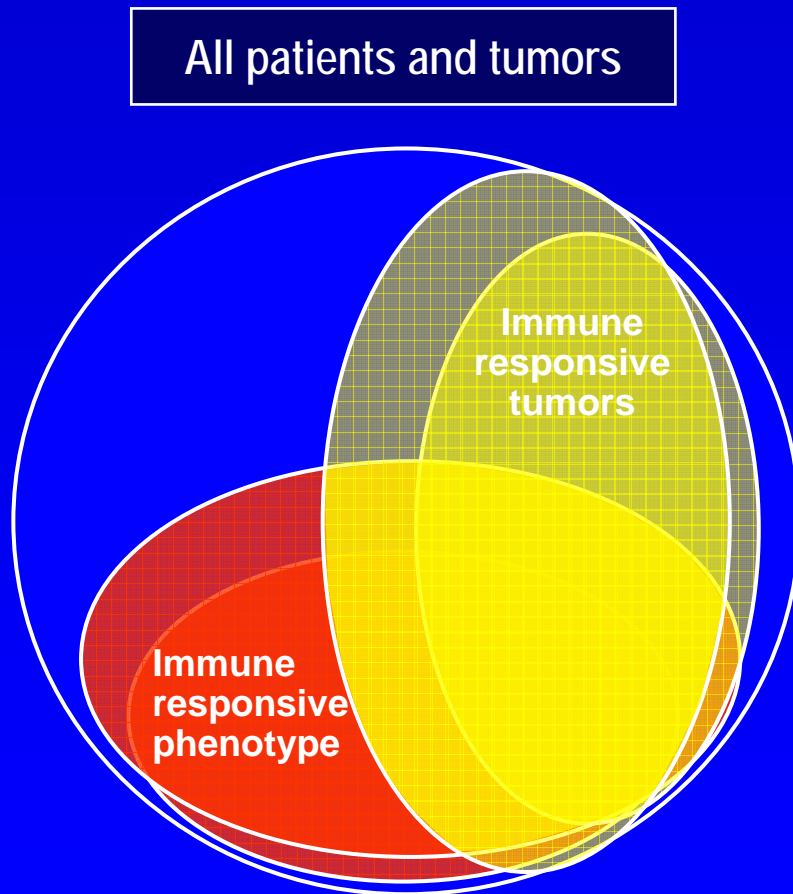
All patients



All tumors



Immunotherapy Selection Model



Immune responsiveness

Higher doses
Elimination of Tregs
CTLA4Ab
CD137 agonist Ab

Tumor Responsiveness

B7H1 Ab
n-methyltryptophan
Earlier therapy

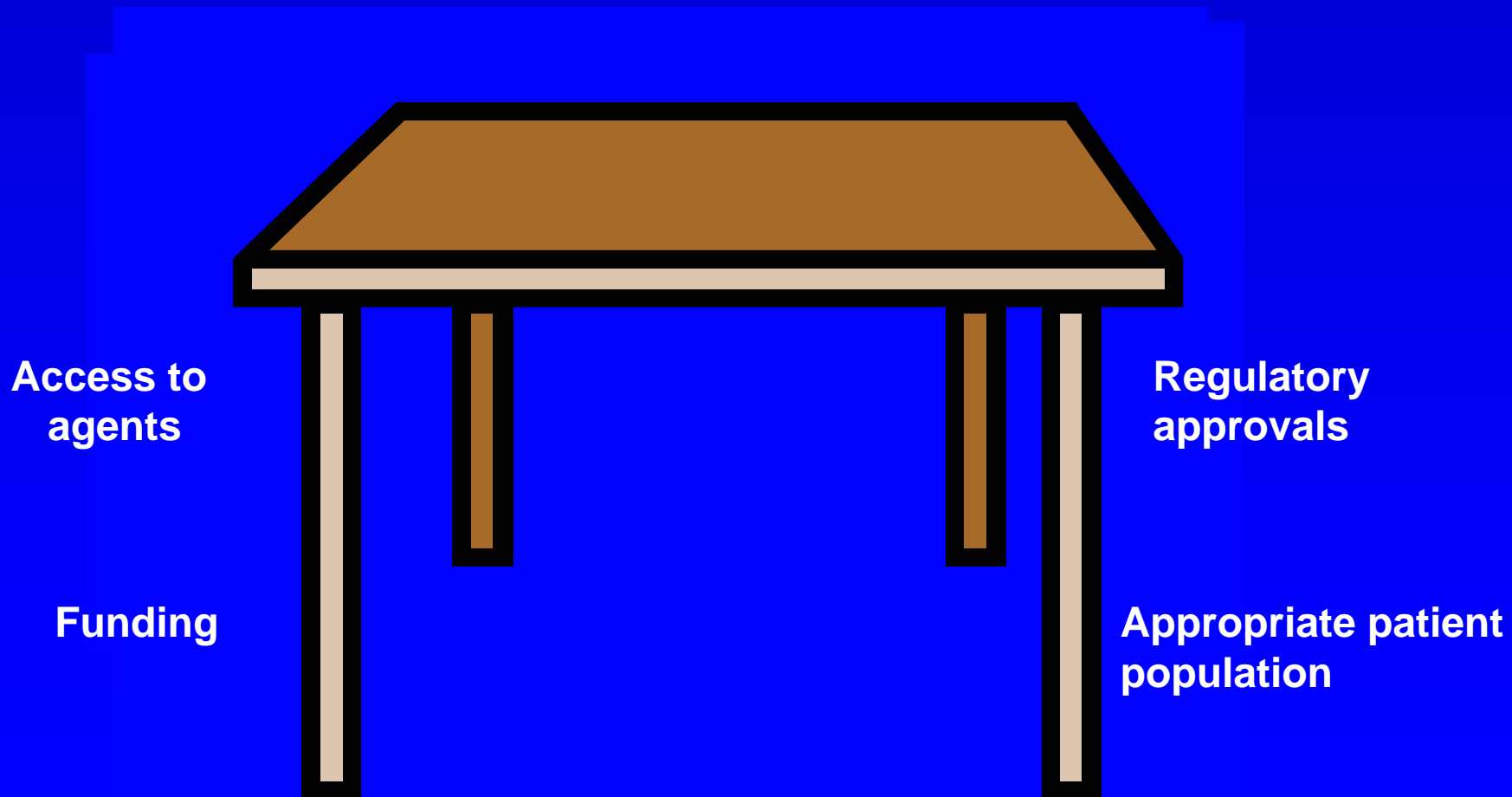
Focus Response

Vaccine

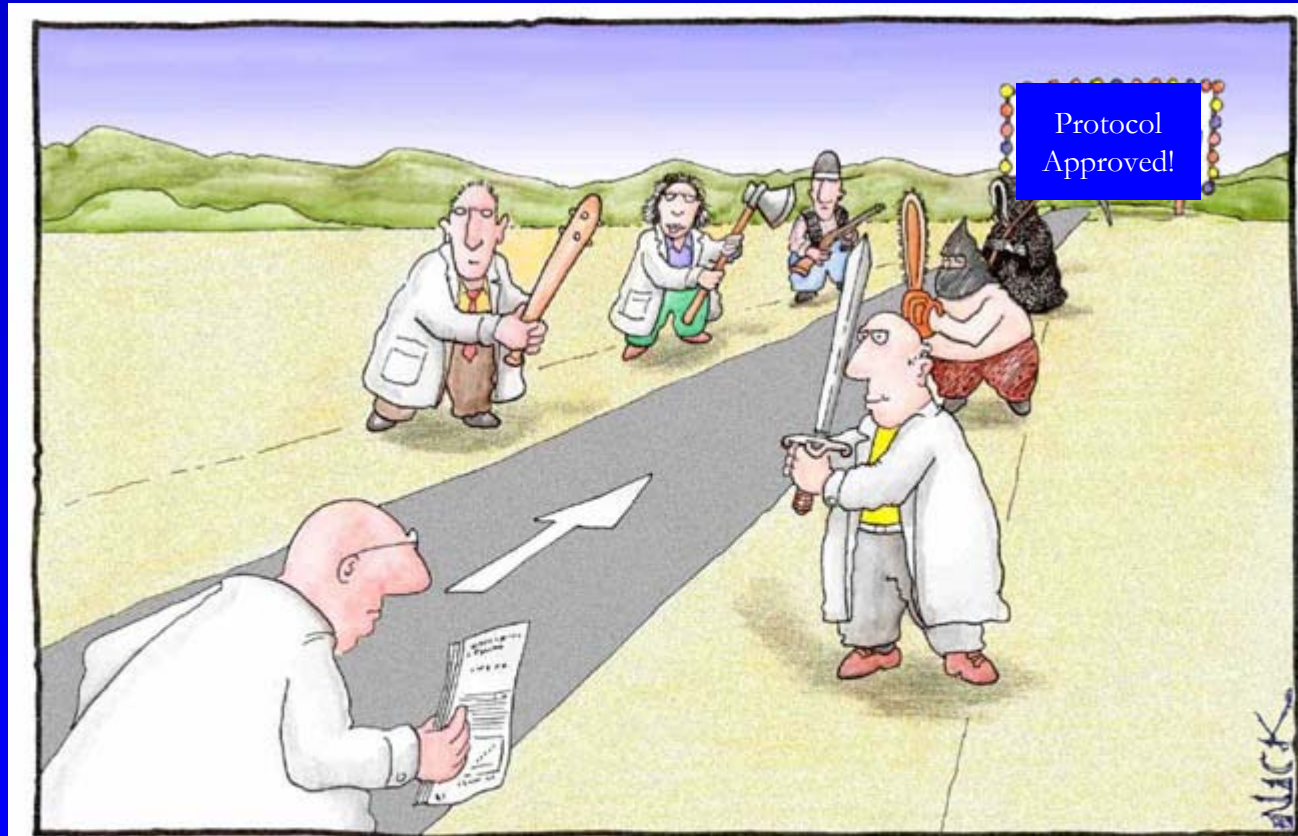
Selection

Identify the patients in the overlap

Translational Research Requirements

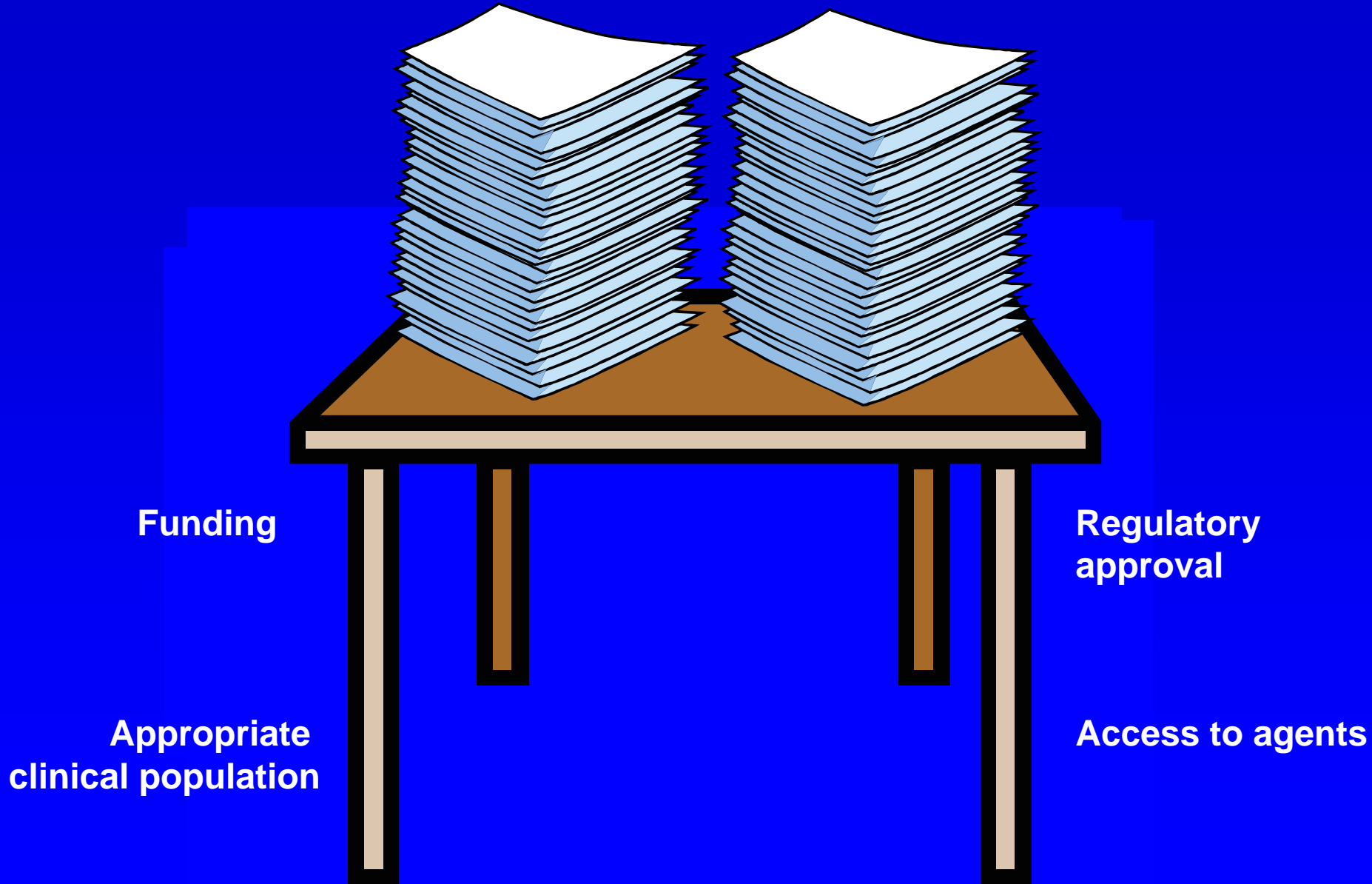


Combination Biologic Therapy Requirements



Most scientists regarded the new streamlined protocol review process as 'quite an improvement.'

Combination Biologic Therapy Research

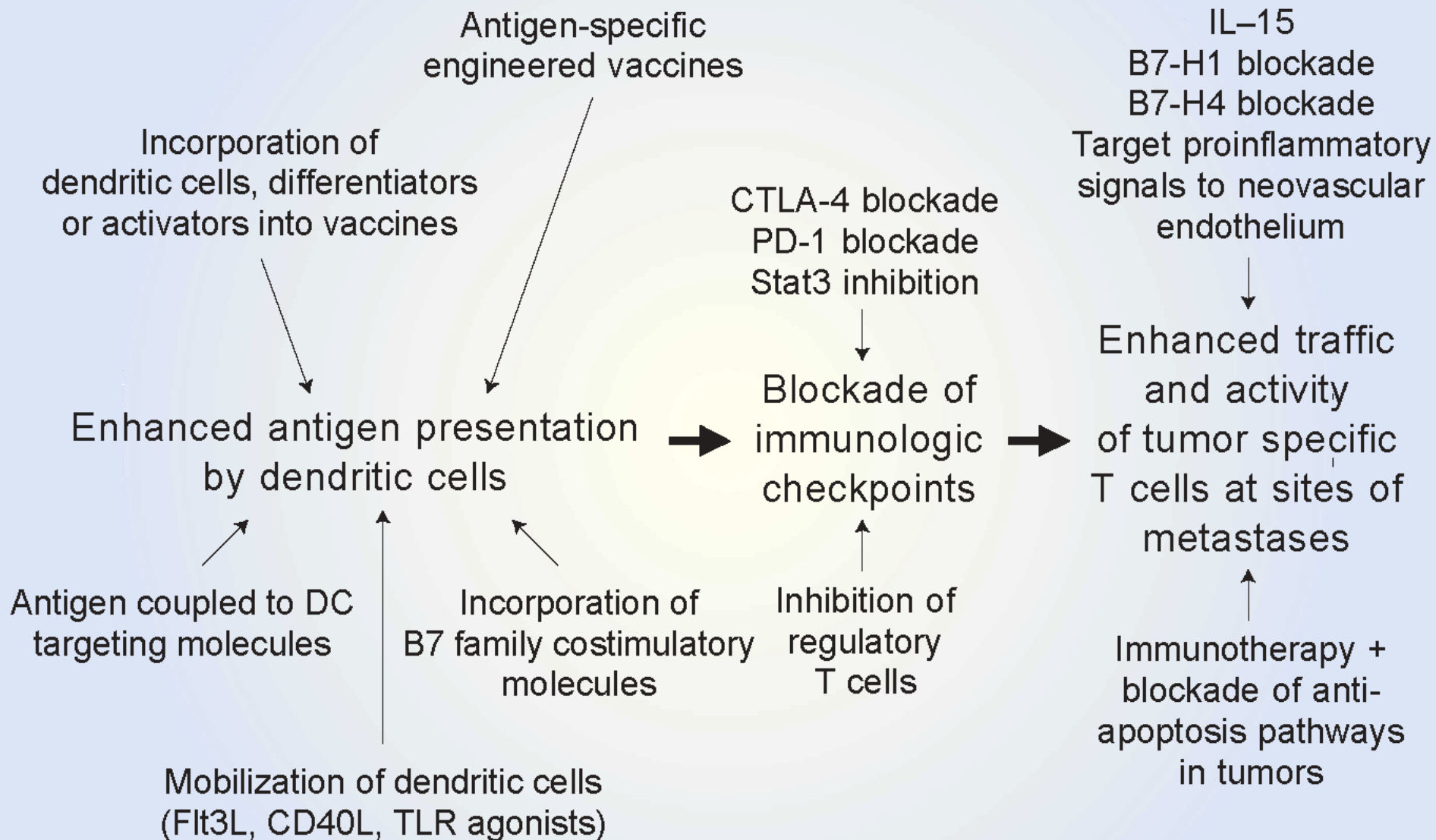


Cancer immunotherapy: breaking the barriers to harvest the crop

Drew Pardoll & James Allison

Successful translation of modern molecular immunology into effective cancer immunotherapy is threatened by regulatory barriers and challenges to the development of novel agents and combinatorial strategies through effective public-private partnerships. For its promise to be fully realized, both the National Cancer Institute and Food and Drug Administration must take active steps to help academic investigators and companies jointly navigate the pathways from laboratory to clinic.

Opportunities to Intervene in Combination Immunotherapy



Combination Biologic Therapy

Barriers-Access to Agents

- ◆ Combining experimental agents difficult
 - IP issues with two companies
 - MTA difficult to get for pre-clinical studies
 - Liability issues with combinations
 - Concerns about toxicity from combination negatively impacting development of single agents
 - More than double the contracting issues
 - Registration path less clear
- ◆ Many potentially active agents are “mothballed” due to lack of single agent activity
- ◆ RAID mechanism is underfunded, understaffed, and uses antiquated technology
 - Slow – (S)AID - 6 compounds produced in first 5 years
 - Unable to make compounds that are under industry patents
 - No “off” switch

Combination Biologic Therapy Barriers-Patient Population

- ◆ Treatments less likely to work in patients with advanced disease
 - Unable to immunize due to immune suppression
 - Inability to give multiple vaccinations
- ◆ Adjuvant treatment approaches require surrogate markers or larger randomized controlled studies
- ◆ Complex adjuvant treatments in patients who might be cured are harder to justify; less willingness to accept toxicity and risk

Combination Biologic Therapy

Barriers-Regulatory Issues

- ◆ FDA doesn't have standard way of dealing with these combinations
- ◆ Drug manufacturing, standardization and safety testing can eat up entire protocol budget
- ◆ Investigator ends up holding the IND for investigator-initiated trials
 - Not adequately trained to handle CRO role
 - All AEs need to be reported
 - Inadequate funding for audits and frequent communication

Combination Biologic Therapy

Barriers-Funding

- ◆ Need funding to support trial and correlatives
 - Costs increased due to increased regulatory burden; requirement for holding IND
 - Correlative endpoints, immune activation, may be major endpoints in trials where response is rare
 - Funding opportunities diminished
 - CTEP approval does not come with much if any funding
 - Absolute decrease in NIH budget
 - Preference for targeted therapies
 - cleaner hypotheses
 - More likely to have preclinical data

Having a Target is preferred



"Bummer of a birthmark, Hal"

Combination Biologic Therapy: Potential Solutions (1)

- ◆ Develop IP template language agreed to by NCI, Universities and Industry
- ◆ Enhance coordination of efforts between NCI, FDA and Industry
 - Allow for funding, drug availability, and trial approval to coincide with clinical research imperatives
 - Create Decision Network to recommend pursuit of promising combinations (Pardoll and Allison)
- ◆ Provide incentives and liability protection to industry for provision of access to potentially promising drugs or allowing agents to be combined (? patent extension)
- ◆ Increase CTEP involvement in negotiating contracts for combinations
 - MTAs
 - INDS

Combination Biologic Therapy: Potential Solutions (2)

- ◆ Design more relevant animal models
 - Ability to test for synergy or inhibitory effects
 - Rationally design combinations
- ◆ More informed correlative studies
 - Monitoring Cores
 - Standardized techniques
- ◆ More TRI funding (?pooled industry, NCI, Foundation support)

Combination Biologic Therapy: Potential Solutions (3)

- ◆ Tailor FDA regulatory burden to disease severity; risk-relaxed AE reporting and eligibility criteria for pts with advanced cancer
- ◆ Modernize and increase funding for RAID or support alternative GMP facilities – prioritize, review
- ◆ Consider unique study populations and designs-
 - regional immunotherapy with SLN assessment
 - Selected/enriched patients populations
 - Early into randomized studies (benchmarked)
 - Smaller studies- bigger differences (Phase III screening trials)
- ◆ Focus on combinations with “targeted” biologic agents
 - Antibodies to immunoregulatory molecules
 - CTLA4, B7H1, B7H4, CD137
 - T-regs

Combination Biologic Therapy: Potential Solutions (4)

◆ Increase Career Development efforts

- Encourage the next crop of clinical / translational immunotherapy investigators
- Multidisciplinary educational and research training programs are needed. "Silos" often create barriers

◆ Build Multidisciplinary teams

- Align the reward system in academic health centers to promote translational and multidisciplinary research
- Increase rewards for collaborative research, collaborative grants, and publications

◆ Provide better public and scientific relations

- "Immunotherapy is a chance for cure"
- Analogy to Whipple procedure for pancreatic cancer
- Accept results of prior phase III trials as "proof of principle"

◆ Enhanced investigator education

- ISBTC Annual Meetings and Workshops

International Society for Biological Therapy of Cancer



21st Annual Meeting

October 26-29, 2006

Hyatt Regency Century Plaza
Century City, Los Angeles, California

Preliminary Program

Abstract Deadline: July 17, 2006



Mini-Symposium on Biologic Effects of Targeted Therapeutics

Thursday, October 26, 2006 · 1:00 pm – 5:30 pm

(Separate Registration Fee Required)

The second of iSBT's concurrent Thursday programs is the Mini-Symposium on Biologic Effects of Targeted Therapeutics. The past two years have witnessed the approval of several agents that target various pathways within tumor cells. A number of these agents also inhibit similar or related pathways within immune cells, endothelial cells and tumor stroma. These "off target" biologic effects may influence the tolerability, activity, duration of benefit and ability to combine these agents. Most information concerning these biologic effects has only recently been identified and much remains to be discovered. This information may greatly impact the use and ultimate effectiveness of these agents. Through this Mini-Symposium, we will seek to present the current state of knowledge and therefore raise consciousness about this area that critically impacts investigation and clinical use of targeted therapeutics both alone and in combination.

The Mini-Symposium will bring together a distinguished faculty of clinical investigators and basic scientists who will present their preliminary data on various aspects of this field. Considerable time will be left for general discussion on the impact of these results on clinical investigations involving combinations of targeted and biologic agents. The end product of this effort will be a publication describing the current "State-of-the-Art" and a roadmap for how research in this field should proceed. This meeting provides not only the opportunity to hear about the latest developments in this fast developing field, but also a chance to interact with colleagues from various disciplines to discuss and shape future investigations and initiate and/or continue fruitful collaborations. The tentative Mini-Symposium schedule is as follows.

Mini-Symposium Topics *subject to change*

Introductions

Impact of Chemotherapy on Angiogenesis

Impact of the Nature of Cell Death on Immune Function

Does Antibody Therapy Induce Immune Response?

Effects of Antiangiogenic Therapy on the Immune System

Off Target Biologic Effects on Targeted Therapies

Impact of Epigenetic Modulators on Biological Properties

Discussion: Impact on Combinations of Targeted and Biologic Therapies

Wrap-Up

Co-Chairs:

Michael B. Atkins, MD

Beth Israel Deaconess Medical Center
Boston, MA

Louis M. Weiner, MD

Fox Chase Cancer Center
Philadelphia, PA

Participating Faculty:

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Mark S. Ernstoff, MD

Dartmouth-Hitchcock Medical Center

Thomas F. Gajewski, MD, PhD

University of Chicago

Peter Jones, PhD

USC/Norris Comprehensive Cancer Center

Robert S. Kerbel, PhD

University of Toronto

Michael T. Lotze, MD

University of Pittsburgh

Walter J. Storkus, PhD

University of Pittsburgh

Pardoll and Allison Scenarios

a

Combinatorial development of two agents—one being produced by company X and the other in the public domain

Academic investigator demonstrates preclinical efficacy of combination of agent A (owned by company X) and agent B (in public domain)



NCI decision :
network advises
trials with A + B



NCI director and FDA
commissioner jointly
contact company X to
discuss liability protection
and payment to company
for additional production of A
for combinatorial trials with B



Combinatorial trials (A + B)
demonstrate efficacy
in phase 1/2 trials



NCI offers license and production
information for agent B to company X
for production in combination with agent A



NCI produces enough clinical
grade agent B for combinatorial
trials with agent A



Pardoll and Allison Scenarios

b

Combinatorial development of two agents—one owned by company X but not being developed and the other in the public domain

Academic investigator demonstrates preclinical efficacy of combination of agent A (owned by company X) and agent B (in public domain)

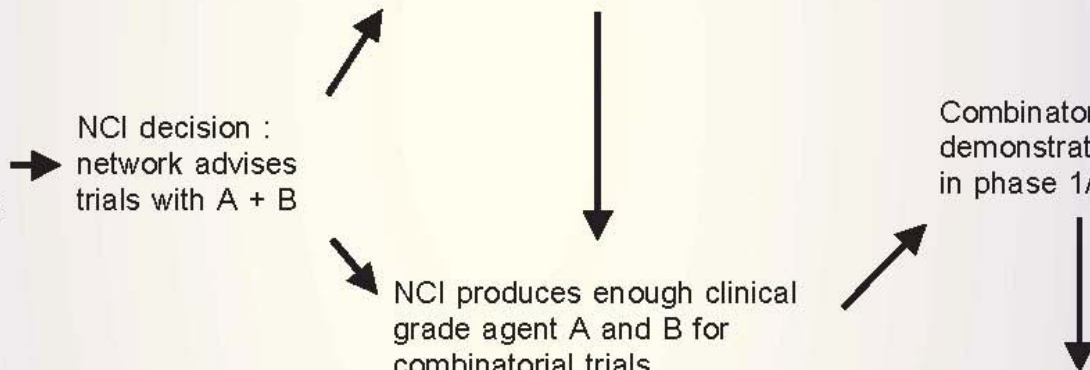
NCI decision : network advises trials with A + B

NCI director and FDA commissioner jointly contact company X to discuss liability protection and transfer of production technology for agent A to NCI

NCI produces enough clinical grade agent A and B for combinatorial trials

Combinatorial trials (A + B) demonstrate efficacy in phase 1/2 trials

NCI offers license and production information for agent B to company X for production in combination with agent A. If company X still not interested, sublicensing to another company is aggressively pursued.



Pardoll and Allison Scenario

C

Combinatorial development of two agents—one owned by company X and the other owned by company Y

Academic investigator demonstrates preclinical efficacy of combination of agent A (owned by company X) and agent B (owned by company Y)



NCI decision : network advises trials with A + B



NCI director and FDA commissioner jointly contact company X and company Y to discuss liability protection and support for combinatorial trials such that companies A and B are incentivized to work together with NCI



Combinatorial trials (A + B) demonstrate efficacy in phase 1/2 trials



Fueled by success of phase 1/2 trials, companies A and B negotiate a joint development plan

Acknowledgements

- ◆ Walt Urba
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- ◆ Jim Yang
- ◆ Drew Pardoll
- ◆ Jim Allison