
Report on the iSBTc Mini-symposium on Biologics Effects of Targeted Therapeutics

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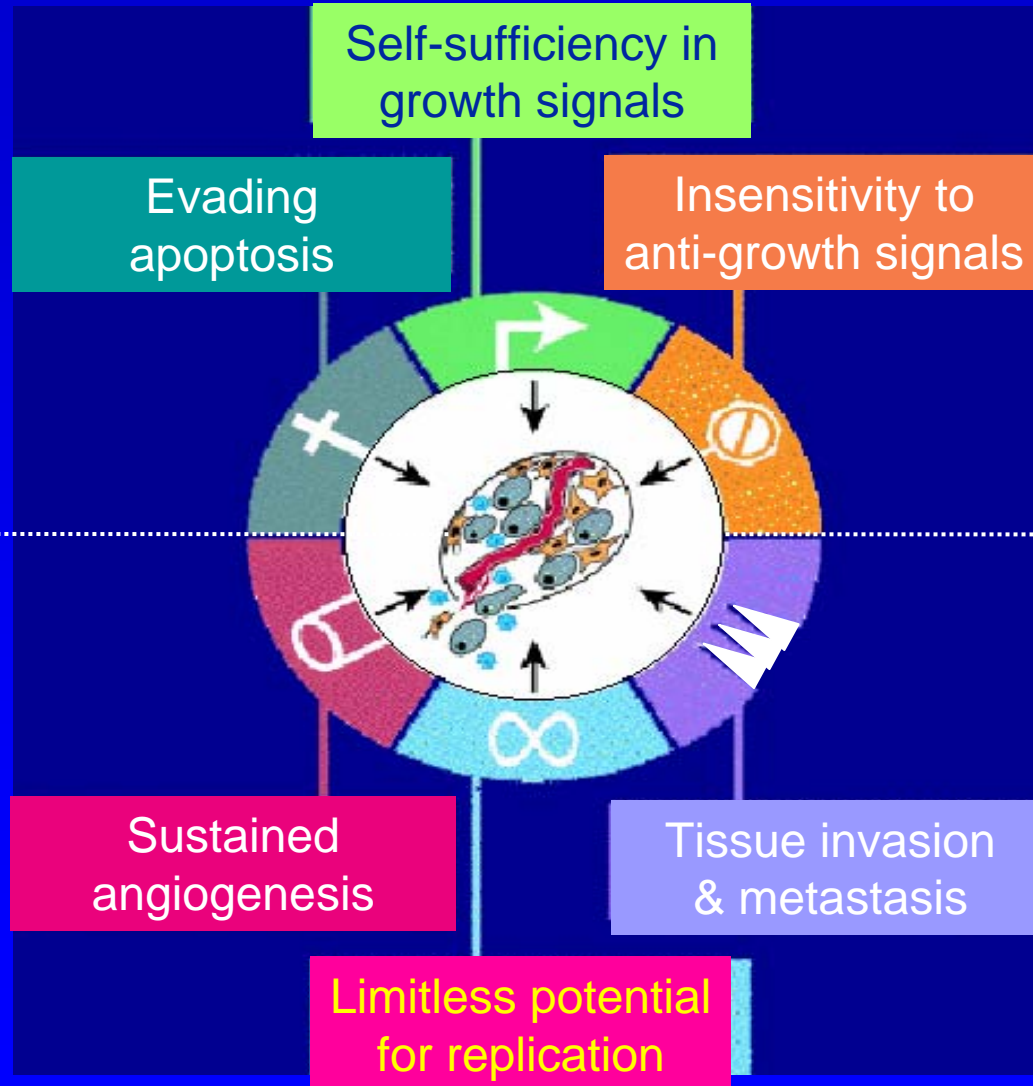
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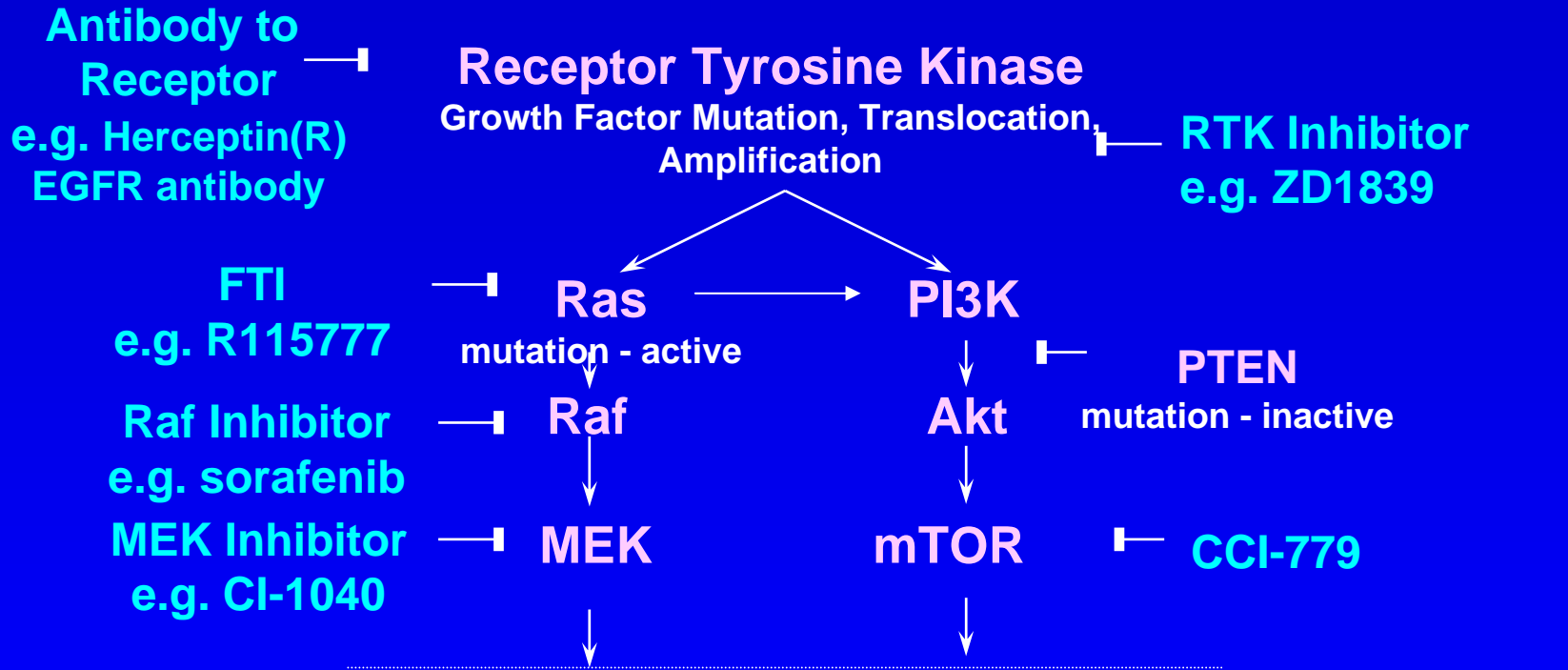
Evolution of Cancer Therapy

- ◆ 1880- Surgery
- ◆ 1920- Radiation Therapy
- ◆ 1970s -Cytotoxic chemotherapy
- ◆ 1985 - Immunotherapy
- ◆ 2000 – Targeted Therapy

Essential Alterations in Cell Physiology in Malignancy



Targets and Tools



Cell Proliferation

Survival

Migration

Angiogenesis

CDK Inhibitor
e.g. Flavopiridol

BCL-2 Inhibitor
e.g. G3139

MET Inhibitor
Src Inhibitor

VEGF Inhibitor
e.g. Bevacizumab

Targeted Therapy: Promise and Progress

◆ Antibodies

- trastuzimab, bevacizumab, rituximab, cetuximab

◆ Small molecules

- C-Kit- imatinib
- VEGFR: sunitinib, sorafenib
- EGFR: gefitinib, erlotinib
- mTOR: temsirolimus

◆ Demethylating agents

- decitabene

Having a target is good



"Bummer of a birthmark, Hal"

Targeted Therapy: Issues (1)

- ◆ Pathways are relevant to more than just tumor cells
 - Endothelium
 - Pericytes
 - Immune cells- DCs, Tcells, Tregs
- ◆ Small molecule RTK inhibitors are less selective than originally anticipated
 - Sorafenib, sunitinib
 - Herceptin- VEGF
- ◆ Blocking some targets may produce pro-survival effects
 - GSK3 β activation
 - Compensatory increases in upstream molecules -
 - HIF related proteins with VEGFR inhibition
 - AKT with mTOR blockade
- ◆ Cell death may trigger distinct biologic pathways

Targeted Therapy: Issues

Off target biologic effects off targeted therapies may influence the tolerability, activity, duration of benefit, and ability to combine these agents

Targeted Therapy: Issues (2)

- ◆ Treatments are largely non-curative
- ◆ Durable complete responses will likely require tumor specific immune activation
- ◆ Consequently, there is interest in combination targeted therapy and immunotherapy therapy

Mini-Symposium: Goals

- ◆ Describe the current knowledge regarding various off-target effects of current therapies
- ◆ Identify most relevant issues and current gaps in knowledge base
- ◆ Discuss optimal means of obtaining necessary information
- ◆ Use above information to -
 - Inform and influence basic science efforts and discussions
 - Rationally design combination treatment regimens
 - Optimally design most relevant correlative studies in the context of current and future treatments

Mini-Symposium

- ◆ Held: October 26, 2006 in Los Angeles



Save the Date

21st Annual Meeting

October 26-29, 2006

Hyatt Regency Century Plaza
Century City, Los Angeles, California

International Society for Biological Therapy of Cancer



Mini-Symposium

Report published Journal of Immunotherapy
September, 2007

Report on the ISBTC Mini-symposium on Biologic Effects of
Targeted Therapeutics.

Atkins MB, Carbone D, Coukos G, Dhodapkar M, Ernstoff MS,
Finke J, Gajewski TF, Gollob JA, Lotze M, Storkus W, Weiner
LS.

J Immunother 2007, 30:577-90.

Mini-Symposium: Topics

- ◆ Impact of antitumor monoclonal Ab Rx on Ag presentation and adaptive immunity
- ◆ Effects of antiangiogenic / targeted therapy on the immune system
- ◆ Impact of cytotoxic chemotherapy on angiogenesis and immune function
- ◆ Combination antiangiogenic and immunotherapy at the clinical level
- ◆ Effect of TKIs on Tregs
- ◆ Impact of FTIs and other targeted agents on T cell activation
- ◆ Impact of epigenetic modulators on biologic properties
- ◆ Impact of the nature of cell death on the immune system

Mini-Symposium: Brief Summary

Complexity

- ◆ Most agents (targets) have multiple (pleiotropic effects)
- ◆ Downstream effects also occur which may be additive or compensatory
- ◆ Even agents in the same class may have distinct off target effects (e.g. sorafenib and sunitinib)

- ◆ “It is not what you know, but understanding the extent of what you don’t know, that is important”

Complexity (2)

- ◆ Effects of targeted agents may vary depending on the tumor type
- ◆ The effects on stroma may also be different as the stroma is often influenced by the tumor cells
- ◆ Biologic effects may vary in distinct hosts
 - Polymorphisms in Fc receptor- Dhodapkar, Levy
 - Propensity to autoimmunity (? CTLA4 polymorphisms, MHC molecules)

Interrelationship exists between pro-angiogenic and immunosuppressive effects

- ◆ Both Cox2 and VEGF are driven by HIF-hypoxia (Carbone)
 - Vascular leukocytes may be induced by VEGF (Coulkos)
 - Cells may have immunosuppressive properties (Cox 2, PGE2, Arginase) (Ochoa)
 - Represent therapeutic targets that could block angiogenesis and improve immune suppression
 - Creates potential role for debulking therapies in advance of immunotherapy
- ◆ Interference with VEGF has positive consequences for immune function
 - What are the sources of this improvement? (T cells, DCs)
 - Are these changes distinct from clinical benefit?
 - Are there rebound, compensatory effects that might minimize this improvement?

Measuring Immune Effects of Various Drugs (1)

- ◆ Effects can be variable and difficult to assess
 - Finke showed diminished Treg numbers with sunitinib
 - Discordant effect with sorafenib
 - Gajewski showed loss of immune function with FTIs

Measuring Immune Effects of Various Drugs (2)

- ◆ Assessment of cell numbers does not imply functional differences
 - Need to assess relationship between phenotype and function
 - Need to know if effects on immune response are specific or general
 - Requires novel assay techniques

Measuring Immune Effects of Various Drugs (3)

- ◆ Need to develop standards for performing these assays
 - Small molecules may have transient effects on targets that may be reversed by washing cells in vitro
 - Assays that involve fresh unwashed cells are more difficult
 - Adding small molecule inhibitors to assays also difficult, may influence targets and well as effectors

- ◆ Need to know relationship with clinical benefit
 - Are changes a direct effect of the treatment or a result of tumor shrinkage (Finke)
 - May require treatment of patients without cancers (adjuvant therapy, inflammatory conditions) to assess
 - Neoadjuvant studies may assess the effect of therapies on the tumor microenvironment rather than in the blood

Measuring Immune Effects of Various Drugs (4)

Having accurate assessment of immune effects are essential for rational combination drug development

Incorporating testing of immune effects into targeted therapy trials is important and creates opportunities for collaboration

Development of Better Animal Models

- ◆ Encourage testing of targeted treatments in an immune competent host
- ◆ Need to work with Mouse Models Consortium to develop such models
- ◆ Orthotopic transplants of human tumors may also be useful (measure effects of therapy in relevant organ system)

Mini-Symposium: Conclusions

- ◆ Biologic effects of targeted therapies represents an important area of scientific research
- ◆ Both positive and negative effects are likely and not easy to predict *a priori*
- ◆ Current investigations have only skimmed the surface
- ◆ Many opportunities exist for future investigation
- ◆ Understanding these interactions are critical for rational combinations of targeted therapies and immunotherapy
- ◆ Inclusion of immunotherapy in combination treatments is likely essential to long term disease control