# WORKSHOP ON FUTURE OPPORTUNITIES FOR THE COMBINATION BIOLOGICAL THERAPY OF CANCER

## IMMUNOTHERAPY-IMMUNOTHERAPY COMBINATIONS BREAKOUT SESSION REPORT

**NOVEMBER 1, 2007**
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# MAJOR QUESTIONS DISCUSSED

- What are the most promising combination opportunities irrespective of logistical issues?
- What are the most appropriate clinical endpoints for immunotherapy trials?
- Should we focus on metastatic disease setting? MRD/adjuvant setting?
- Should we thinking about integrating non-immunologic agents that possess immunomodulatory properties?
- Will there be an immunologic cocktail for each patient? Each tumor type? Common themes?
- What non-scientific barriers are limiting progress (legal/IP, reagent availability, regulatory)?

# SCIENTIFIC CONSIDERATIONS

- Consideration of mechanisms to engage non T cell components of immune system
  - Antibody/B Cells
  - NK cells
  - Macrophage subsets
  - Combinations of above
- Immunomodulatory effects of non-immunologic agents
  - VEGF modulation
  - Chemotherapy-induced loading of antigen onto APCs

# TRANSLATIONAL CONSIDERATIONS

- Optimal use of mouse models as preclinical testing ground
  - Good models used the wrong way
  - Application of mouse model data to inappropriate clinical setting
  - Could we create better models that are more predictive?
- Minimal residual disease mouse models
  - Should use as such if planning MRD clinical trial
- Fundamental genetic differences between mouse and human
  - KIRs, TLR9 distribution
  - Concept of “humanized mice”
  - Kinetics of tumor growth in mouse versus man
- Expecting synergy in mouse model to cross threshold for clinical translation
  - What if model chosen is inadequate?
  - What if genetics are different?

# CLINICAL CONSIDERATIONS

- Metastatic versus minimal residual disease setting
  - Metastatic
    - Pros: biopsiable tumor, tumor biology effects (Ag loading, necrosis/inflammation), better risk/benefit, measurable clinical response, faster time to clinical endpoint, smaller sample size
    - Cons: tumor bulk, poor PS, global immunosuppression
  - MRD
    - Pros: less immunosuppression, les tumor bulk
    - Cons: hard to study tumor microenvironment, difficult to assess response, longer clinical endpoints, larger sample size, les favorable risk/benefit
  - Possible compromise? Low volume metastatic disease
- Clinical endpoints for immunotherapy trials
  - Are standard response criteria adequate?
    - Time to response
    - Progression then regression
    - Prolonged stable disease
    - Risk of attributing response to downstream therapy
  - Is objective response the best endpoint?
    - TTP, OS
  - Is there need for a new response assessment tool?
- Biomarkers
  - Gather data early
  - Need favorable and unfavorable clinical outcome patients in order to validate biomarkers as surrogate or predictor
  - This requires resources, effort, patient cooperation—but the scientific need is great
  - Biomarker alone unlikely to gain approval—clinical activity trumps