Session 4: Developing New Therapeutics

Sharpless, Roberts (Duncan presentation unavailable)

May 25, 2011
Overview

Ned Sharpless

May 25, 2011
**Therapeutics Theme Team**

- **Target Identification and Validation**
  - Structural Biology
  - RNAi Screening
  - Proteomics

- **Drug delivery innovation**
  - Nanoparticles
  - Theranostics
  - Novel delivery systems

- **Novel drug discovery**
  - Small molecules
    - High Throughput Screening
    - Computational Approaches
    - Medicinal Chemistry

- **Preclinical Cancer Models**
  - Predict efficacy
  - Test UNC compounds
  - Analyze PK/PD

- **Human clinical trials**

- **CCNE**

- **Pharm/ TOND² / IPIT**

- **CICBDD**

- **MP1U**
Effective use of PI3K and MEK inhibitors to treat Ras mutant and non-mutant cancer

Patrick Roberts, PharmD, PhD
5/25/2011
MP1U House Rules:

- Credential the GEM model
- Primary Endpoints: 21 day response and survival
- “Success” requires tumor regression and prolonged survival
- Routine PK and/or PD
- Use large cohorts (n>15)
- Test old drugs
- Get best new drugs any way you can.
TRIA Melanoma Model

(Tyr-HRas\(^{\text{G}12\text{V}}\) \(\text{Ink4a/Arf}^{\text{-/-}}\))

- Genetics faithful to the human disease (Ras activation and \(\text{Ink4a/Arf} \text{ loss}\))

- Simple genetics assures large colonies of tumor-bearing mice with minimal genotyping.

- Although B-Raf mutations are more common, we choose Ras mutant model given the importance of this target in a wide spectrum of cancers, as well as the difficulty of drugging Ras as opposed to kinases like Raf.
TRIA Melanoma Model is Intrinsically Resistant to Standard Therapy
### TRIA Model Recapitulates Reported Human Response Rates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean day 0 tumor volume (mm³)</th>
<th>Mean day 21 tumor volume (mm³)</th>
<th>Response Rate by RECIST at 21 Days (CR+PR+SD)</th>
<th>Reported Human response rates for melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>83</td>
<td>322</td>
<td>0%</td>
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<td>Temozolomide</td>
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<td>15% (10-17%)</td>
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Simplified Ras Signaling Pathway

RTK (EGFR, KIT, MET) → RAS → B-RAF

Mutated in 30% of all human cancer

PTEN → PI3K

BEZ235

AKT

MEK → ERK

AZD6244
Dual MEK and PI3K Inhibition Elicits TRIA Tumor Regression

Day 21 Percent Change in Tumor Volume (%)
## Promising Results!

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<td>56%</td>
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Day 21 Response Correlates with Increased Survival

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<th>Median Survival (Days)</th>
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C3-TAg
Basal-like Breast Cancer Model

Expresses SV40 large T antigen shown to inactivate both p53 and RB. Shown to have frequent K-Ras amplification and infrequent Ras mutations.
MMTV-\(c\)-\textit{neu}

Her2 Positive Breast Cancer Model

Expresses \(c\)-\textit{neu} (the mouse ortholog of human HER2).
T11
Claudin-low Breast Cancer Model

An orthotopic P53 null Breast Cancer model which has a similar gene expression profile to the human claudin-low breast cancer subtype.
Summary

- GEMM testing at UNC is highly advanced
- We have identified dual MEK/PI3K inhibition as a promising treatment approach for Ras-mutant and non-mutant cancer.
- We have initiated industry collaborations to test other MEK and PI3K inhibitors with varying isoform selectivity.
- We are always looking for new collaborators!
THANK YOU!!

- David Darr
- Jerry Usary
- Patrick Dillon
- Kat Bendt
- Kelly Clark
- Jamie Jordan
- Lorraine Balletta
- Austin Combest
- Suzan Hanna
- Norman Sharpless
- Chuck Perou
- Bill Zamboni