iSBTc Combination Therapies Workshop
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Industry Perspective

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Business: a three-legged stool

Risk

Time

Cost/Return
The perfect drug development candidate – early development

• Highly predictive preclinical models
  – Pharmacology and physiological signal highly parallels that in humans
  – Manifest biomarkers of efficacy and safety
• Demonstration of proof-of-concept in Phase I
  – Biomarkers
  – Obvious physiological signal
• Advantageous dose- and schedule-finding in Phase II
  – Large effect size with rapid onset of effect
  – Treatment-naïve experimental subjects
The perfect drug development candidate – late-stage development

- High signal-to-noise ratio in Phase III
  - Plentiful treatment-naïve subjects
  - Large effect size with rapid onset of effect and inexpensive endpoints
  - Predictable pharmacological, PK and physiological effects
- Established regulatory guidelines
- Large numbers of patients with high unmet needs
- Undisputed, exclusive intellectual property position
- 100% ownership of the development asset with few competitors
Doubly blessed – “ideal combinations” are some of the industry’s most successful products

• “Mechanistic” combinations
  – *Augmentin* (amoxycillin + clavulanate)
  – *Bactrim/Seprin* (trimethoprim + sulphamethoxazole)

• “Own bundle” combinations
  – *Advair* (salmeterol + fluticasone)
  – *Lotrel* (amlodipine + benazepril)

• “Hands across the water” combinations
  – *Vytorin* (ezetimibe + simvastatin)
Cold hard reality

Doubly cursed: Biological combinations for cancer
The nightmare drug development candidate – early development

• Poorly predictive preclinical models
  – No natural models resembling human disease
  – No identifiable reliable biomarkers

• Little to go on in Phase I
  – No biomarkers
  – No obvious physiological signal

• Disadvantageous dose- and schedule-finding in Phase II
  – Small- to non-existent effect size
  – Multiply-pretreated experimental subjects in poor condition
  – Need to rely on larger controlled studies for proof-of-concept
  – Expensive and/or time-consuming endpoints
The nightmare drug development candidate – late-stage development

- Low signal-to-noise ratio in Phase III
  - Heavily pretreated subjects
  - Modest effect size with late readout – eg, survival
  - Pharmacological, PK and physiological effects not obvious

- Demanding, unclear regulatory guidelines
- Patients subdivided by disease and stage
- Disputed and/or shared intellectual property position
- Shared ownership of the development asset
The appeal to industry of biologic combinations in cancer

• Large unmet medical need
  – Most therapies have modest effects
  – Large premium on maximizing efficacy with multiple therapies

• Recent successes – just the beginning?

• Promising science
  – Multiple novel mechanisms of action in cancer
  – “Big protein” targets accessible to biological therapies
  – Few off-target effects
  – Expanding/maturing biologics technologies
  – Logical reasons to expect combinations to add/synergize
  – Past tradition of combination therapies

• Highly supportive regulatory and academic infrastructure

• Combinations create an added IP dimension
Challenge #1: Intellectual property

• Ownership of IP is arguably the driving force of academic and industry innovative success

• Some issues
  – IP ownership is a social and political construct under challenge
  – IP is increasingly fragmented and ill-defined
  – Competition for IP ownership can create conflicting goals, eg of industry and academia
  – Development time and cost expansion can erode the value of IP
Challenge #2: Getting along

• How to play the combo game when none of the participants will show its hand?
  – Access to “on-the-shelf” assets
  – Sheer volume of permutations
  – Incentives and disincentives
    • IP
    • Contracts
  – Industry and academia – different worlds or getting too much alike?
Challenge #3: Regulation and decisions

• Endpoints
  – For proof-of-principle – can you know before Phase III?
  – For approval

• Potency assays

• Pre-clinical safety testing
  – If the toxicology of one agent is difficult to model, try two

• Combinations - proof of contribution of components
  – When one or both components are ineffective alone?
    • Pre-clinical
    • Early clinical
    • Late clinical
Challenge #4: Getting things done

• Patient access
  – Numbers are limited
  – Long-term and low-signal-strength outcomes further restrict availability
  – Cancer is not the common cold

• Oversight by IRBs, scientific review and attorneys
  – Time-consuming and burdensome?

• Endpoints – are we hitting the Heisenberg Principle?