iSBTc Combination Therapies Workshop

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Industry Perspective

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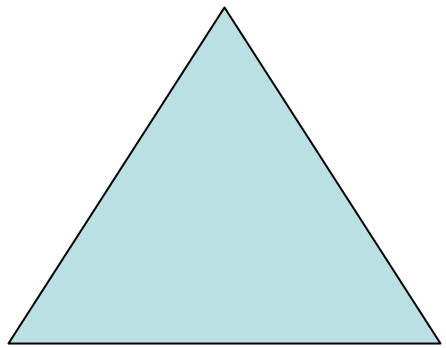
Business: a three-legged stool

Risk



Time **Cost/Return**

The perfect drug development candidate – early development

- Highly predictive preclinical models
  - Pharmacology ans 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/Septrin* (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?