Academic and Industry Partnerships

Technology Transfer and Scale-Up

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Disclosure

- Stewart Abbot is an employee and shareholder of Fate Therapeutics Inc.

- Fate Therapeutics Inc. has an ongoing collaboration with the Regents of the University of Minnesota
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Technology Transfer

Guiding principles

• Ask not what your partner can do for you, but what you can do for your partner
  – after all it’s a marriage…of sorts
• Bear in mind that each partner may have different priorities
  – Publications
  – Patents
  – Trade-secrets
  – Risk-tolerance
  – Timelines
  – Funding
• Assume it the process will take longer than the initial Gantt chart
• TPPs are useful
  – Target Product Profile
  – Target Process Profile
• Put the patients first

Target Product and Process Profiles

• A basic statement of expectations of product form and function
• US FDA “The TPP embodies the notion of beginning with the goal in mind”
• Selected Attributes: T Product P’s
  – Product description: Brief description and/or current product name
  – Mechanism of action: The mechanism by which the product produces an effect on a living organism (Efficacy / Potency).
  – Indication for use:
  – Expected Doses
• Selected Attributes: T Process P’s
  – Process “feedstock”
  – Process yields
  – Process / product identity & purity
  – Process residuals
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Technology Transfer

Key Considerations (Context: IND and FIH study enablement)

- **Direction of Technology Transfer**
  - Technology developed in academic setting transferred to commercial partner or license holder
  - R&D conducted in a commercial setting transferred to an academic partner for clinical manufacture and clinical trial

- **Stage and Environment of Development**
  - Stage of technology R&D prior to transfer
    - Level of process understanding
  - Expected / necessary stage of development after transfer
    - i.e. what level of process development will be required during "transfer"
  - Expected time required for process development / transfer
  - Academic R&D environment ≠ Biotech R&D Environment ≠ Pharma R&D Environment
    - Process Understanding, nature, and level of documentation

- **Elements to be Transferred**
  - Process complexity
    - Process AND Process QC

Challenges and Approaches

- **Typical Challenges**
  - Overestimation of process understanding and control prior to transfer
  - Technology transfer is a great way of finding out what elements of a process are variable / not sufficiently controlled
  - Potential need to conduct "process development" during transfer
  - "Language" barriers e.g. different understanding of TLAs (QBD, CTQ, TRL etc.)
  - Aggressive sponsor timelines
  - Forgetting that QC assays may have to be transferred ahead of the process

- **Typical Approaches (assumes legal agreements in place)**
  - Transfer and review process documentation
    1. Research, Development, Manufacturing, QC & QA
    - Mutual definition of success metrics is CRITICALLY important
    2. On-site review and performance of process at site of process establishment ("see one" or more)
    3. On-site review and performance of process at site of process establishment ("do one" or more)
      - Perform engineering runs (selected unit operations or entire process)
      - Perform Process Qualification (PQ) runs on entire process
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Process Scale-Up & Scale-Out

Terminology

• Scale-up e.g. monoclonal antibodies
  – Traditional approach to creating product supply for clinical studies
  – Few product batches created at an ever increasing scale of production
  – Few manufacturing centers with national / international distribution

• Scale-out e.g. HSCT
  – Increasingly popular approach for patient-specific therapies
  – Ever increasing number of product batches created at a similar (single-patient) scale of production
  – Potential for multiple manufacturing centers with national / international distribution

Scale-up versus Scale-out (excluding ultra-orphan indications)

• Phase 0/1 studies: ~12 patients
  – Single or few clinical sites within country
• Phase 2 studies: 60+ patients ± control population
  – >1 potentially 10s of sites in different countries
• Phase 3 studies: 100+ patients ± control population
  – Likely >10s of sites in different countries
• Commercialization: likely 1000’s, 10,000’s of patients
  – Ideally globally
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Types of Processes
• Typical donor or patient-derived therapy
  
  - Whole process is repeated for every patient
    - Requires manufacturing scale-out, ideally with automated unit operations

• Typical highly expanded-allogeneic therapy
  
  - Small part of the process is repeated for every patient
    - Requires manufacturing scale-up (elements in red conducted once / few times per product life)

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Process Scale-Up & Scale-Out

Technologies (Cell-based Therapies)

• Scale-up
  – Increasing use of process analytical technologies
  – Increasing use of complex bioreactors to achieve required scale
  – Predominant use of single use disposable
  – Investment of process-development time to define CQAs to ensure scalability

• Scale-out
  – Increasingly use of automation to achieve throughput and scale
  – Increasing use of simple bioreactors to achieve scale
  – Almost complete reliance on single use-disposable systems
  – Investment of process-development time to define patient-to-patient (batch-to-batch) variability

System / Process Control

– The ability to control a process during scaling can only be as good as the ability to measure the process
– Measurements (QC) should define critical to quality (CQAs) attributes of the process
  • e.g. transduction efficiency, cell expansion, cell identity, product purity & functional attributes (efficacy)
– Long-term process variation should be determined, but might be expected to be ~3x short-term variation
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Process Scale-Up & Scale-Out

### Key Considerations

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<thead>
<tr>
<th></th>
<th>Scale-up</th>
<th>Scale-out</th>
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<tbody>
<tr>
<td>Changes in unit operations with increasing scale</td>
<td>Modest to major</td>
<td>Minor</td>
</tr>
<tr>
<td>Utilization of labor with increasing scale</td>
<td>Increasingly efficient</td>
<td>Modest efficiency gains</td>
</tr>
<tr>
<td>Cost and consequence of batch failure</td>
<td>Major</td>
<td>Minor (depending on indication)</td>
</tr>
<tr>
<td>Process development required to increase scale</td>
<td>Major</td>
<td>Modest</td>
</tr>
<tr>
<td>Quality control</td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td>Compatibility with highly complex processes</td>
<td>High</td>
<td>Low</td>
</tr>
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**Academic and Industry Partnerships Technology Transfer Conclusions**

- Ask not what your partner can do for you, but what you can do for your partner
- Each partner may have different priorities and terminologies
- Assume tech. transfer will take longer than initially expected
- TPPs are useful (start with the end goal in mind)
- The larger the scale (scaled-out or -up) the better the process understanding needs to be to control variation
- When in doubt put the patients first
Thank You

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