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Precision and Biomass Fermentation Scientific Benchmarks, Key Questions and Areas of Novelty

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Scientific Benchmarking Guide for Fermentation Technology Companies

Revised August 30, 2023

Background

When evaluating fermentation technology companies, benchmarks for performance and quality can be set by comparing those of similar stage companies and literature around theoretical maximums. KPI quantification can help streamline deal flow and improve the quality of decisions by standardizing expectations across a range of companies to facilitate discussions among multidisciplinary investment team members. The guide can also help investors lacking experience in the space perform rough estimates and comparisons.

Here, we present a benchmarking guide for precision fermentation technology companies which was constructed using Lever's DD experience and internal fermentation technology database. The guidelines were created for precision fermentation of proteins and can serve as a rough guideline for others in the space. It is important to note that the overall assessment of a company's technology should take into account all related aspects, and not only the ones presented in this guide. While fully quantitative scoring is not possible due to high associated complexity in addition to the presence of intangibles, the following is Lever's first attempt at a semi-quantitative approach for precision fermentation technology scoring. This output streamlines the Lever VC due diligence process, and serves as a robust screening and benchmarking tool to precede other more detailed aspects of our scientific DD.

Lastly, it is worth noting that:

- The guide is compounding, meaning a company at any particular stage is evaluated using the criteria within its corresponding stage as well as criteria in any earlier stages (e.x. A seed-stage company is evaluated using seed and pre-seed/concept criteria).
- These guidelines are based on internal data sets that are largely composed of precision fermentation of dairy and heme proteins. Therefore, the benchmarks around strain optimization, cell densities and volume scales may differ in cases where other proteins are targeted. Naturally there is significant variation between protein characteristics which can affect benchmarks, especially for proteins which are higher in molecular weight or more difficult/complex to express such as gelatin or myosin. Additionally, higher value proteins such as Lactoferrin may tolerate lower titers and lower production volumes which would skew the corresponding benchmarks.
- When applicable/required, common sense scientific and engineering principles aided in the derivation of the criteria.

- The guide is compounding, meaning a company at any particular stage is evaluated using the criteria within its corresponding stage as well as criteria in any earlier stages (e.x. A seed-stage company is evaluated using seed and pre-seed/concept criteria).
- A theoretical proof of concept is defined as a hypothesis which is supported by sufficient existing literature.
- An experimental proof-of-concept is defined as an experimental validation of core concepts in a manner that has high enough similarity to the end application. In some cases, the use of animal derived molecules can be used as a substitute for recombinant ones which have not yet been expressed in sufficient quantities.

Benchmarks for Precision Fermentation Proteins

- Pre-seed / concept stage
    - A novel idea - **expected**
        - A unique idea (ex. New molecule)
        - A method for lower cost of production (ex. Unique syn bio approach)
        - A method for increasing functionality/organoleptics (ex. protein engineering, or DSP formulation)
    - Proof-of-concept
        - Theoretical - **expected**
        - Experimental - **great**
        - Theoretical & experimental – **fantastic**
    - R&D progress
        - Any progress - **expected**
        - Proof of expression - **good**
        - Proof of functionality – **fantastic**
- Seed stage
    - Novelty
        - No novelty and low defensibility - **not good**
        - No novelty and high defensibility - **good if other aspects are good**
        - Novel and low defensibility - **great**
        - Novel and high defensibility – **fantastic**
    - R&D progress
        - Proof of expression - **expected**

- Proof of functionality - **great**
- Strain optimization (titer)
  - ≤ 1 g/L - **early stage**
  - > 1 g/L - **expected**
  - > 5 g/L - **good**
  - > 10 g/L - **great**
  - > 15 g/L – **fantastic**

- Media optimization
  - > 10 USD/L - **early stage**
  - 1-10 USD/L - **good**
  - < 1 USD/L – **great**

- Scale-up
  - USP (per reactor)
    - ≤ 1 L - **not acceptable**
    - > 1 L - **expected** (if titers good enough to justify)
    - > 10 L - **good** (if titers good enough to justify)
    - > 100 L - **great** (if titers good enough to justify)
    - > 1,000 L - **fantastic** (if titers good enough to justify)
  - DSP
    - A realistic plan - **expected**
    - Any tangible accomplishments - **fantastic**

- Product testing
  - No testing - **acceptable**
  - Functionality testing - **great**
  - Organoleptic testing - **great**
  - Customer testing – **fantastic**

- Series A stage

  - Novelty
    - No novelty and low defensibility - **acceptable** if revenue traction is good
    - No novelty and high defensibility - **acceptable** if all other aspects are good
    - Novel and low defensibility - **good**
    - Novel and high defensibility – **great**

  - R&D progress
    - Proof of expression - **expected**
    - Proof of functionality - **expected**
    - Strain optimization (Titer)
      - < 10 g/L - **not acceptable**

- > 10 g/L - **good**
- > 20 g/L - **great**
- > 30 g/L - **fantastic**

- Media optimization (cost)
  - > 10 USD/L - **not acceptable**
  - 1-10 USD/L - **acceptable**
  - < 1 USD/L - **good**
  - < 0.5 USD/L - **great**
  - < 0.2 USD/L – **fantastic**

- Scale-up
  - USP
    - Volume scale (per reactor)
      - < 1L - **not acceptable**
      - 1-10 L - **not acceptable**
      - > 10 L - **expected**
      - > 100 L - **good**
      - >1,000 L - **great**
      - >10,000 L - **fantastic**
    - Cell density
      - > 40 g/L - **expected**
      - > 80 g/L - **good**
      - ≥ 150 g/L – **fantastic**

  - DSP
    - A realistic plan - **expected**
    - Techno Economic modeling - **expected**
    - Lab scale trials - **good**
    - Pilot scale trials – **great**

- Product testing
  - No testing - **not acceptable**
  - Functionality testing - **expected**
  - Organoleptic testing
    - Qualitative and preliminary tasting panels - **expected**
    - Quantitative lab assays - **good**
    - Statistically significant 3rd party / customer tasting – **great**

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Areas of Novelty for Precision Fermentation

- Upstream process
    - More efficient and efficacious methods/models for genetic modification towards improving
        - Titer
        - Compatibility with lower cost feedstocks
        - Proliferation rates
        - Cell densities
    - More efficient and higher throughput methods for organism screening and directed evolution
    - More efficient and efficacious methods for bioreactor conditions at different scales
    - Continuous fermentation systems
    - Automation
    - Lower capital cost bioreactor systems while still retaining high levels of bioprocess control and cleaning/reusability

- Downstream process
    - Upstream process optimization for minimal downstream processing requirements
    - Product formulation/optimization for lowest purity harvest from precision fermentation
    - Lower capital cost solutions
    - Continuous systems
    - Automation
    - Lower energy consumption

- Product
    - An interesting or un-attempted product produced via precision fermentation
    - Functionalities beyond those of animal products
    - Functionalities different from those of animal products
    - Clean label enhancers/alternatives