Development and application of screening scale bioreactor systems for very high cell density perfusion of mammalian cells

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Perfusion culture in mini-bioreactors

**Challenges for mini-bioreactors**
- Cell separation device
- Optimization of oxygenation
- Hydrodynamic optimization
- Feed medium optimization
- Lower lactate accumulation

**Feed medium optimization**
Lactate affect the cell viability and the cell growth
Gradually lower glucose conc. in feed medium → g_m and g_m decreased
Nutrient feeding optimization

**Hydrodynamic optimization**
Shear stress in hollow fiber

**Cell separation device**
Flow of cell broth in one direction and driven by a pump
Flow in alternating direction by a diaphragm pump

**Perfusion with tangential flow filtration in mini-bioreactor**
- Very high cell density ≥ 80 x 10^6 cells/mL
- Viability ≥ 91%
- Volumetric productivity increasing with cell density even at low CSPR ≥ 3 g/L/day
- Cell specific IgG productivity 20-35 pg/cell/day
- Similar cell metabolism
- Similar EPO productivity

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