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9-18-2017

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Recommended Citation

Filipa M. Gonçalves, Leda R. Castilho, and Juliana Coronel, "Use of a biphasic perfusion process based on mild hypothermia for recombinant glucocerebrosidase (GBA) production" in "Integrated Continuous Biomanufacturing III", Suzanne Farid, University College London, United Kingdom Chetan Goudar, Amgen, USA Paula Alves, IBET, Portugal Veena Warikoo, Axcella Health, Inc., USA Eds, ECI Symposium Series, (2017). http://dc.engconfintl.org/biomanufact_iii/87

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Use of a biphasic perfusion process based on mild hypothermia for recombinant glucocerebrosidase (GBA) production

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Glucocerebrosidase (GBA)

- Enzyme used for replacement therapy of Gaucher disease (GD)
- In the market: imiglucerase (Cerezyme®), taliglucerase α, velaglucerase α
- Must be internalized into macrophages through mannose receptors
- Previous work at UFRJ (Brazil) developed GBA-producing clones from different CHO parental cell lines, including glycomutants*

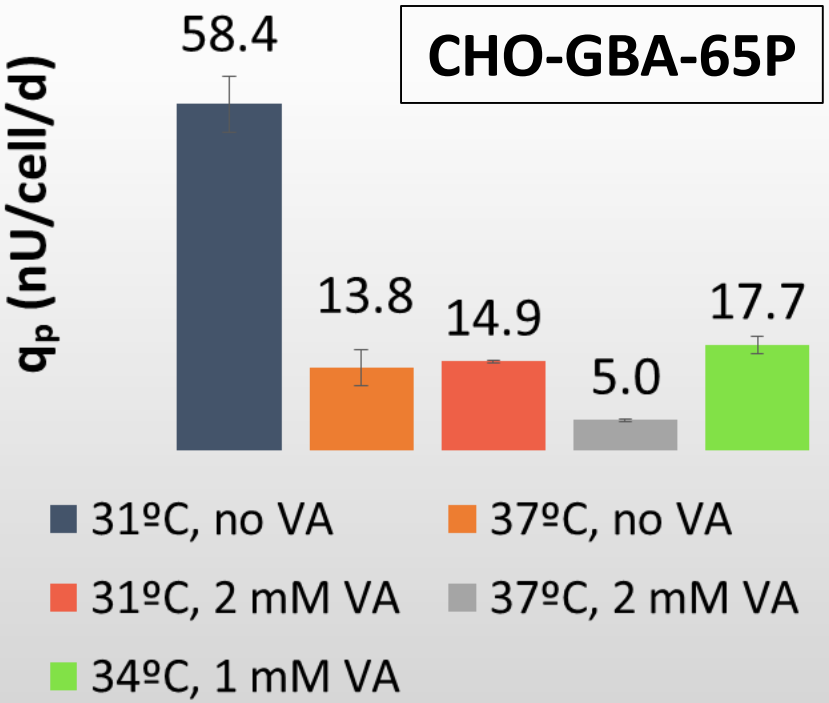
Aims of the work

- Upstream process development based on evaluation of:
  - ✓ temperature reduction
  - ✓ supplementation with a productivity enhancer (valeric acid)
  - ✓ perfusion operation

*parental CHO glycomutants kindly provided by Pamela Stanley (Albert Einstein College of Medicine, USA)

Temperature and valeric acid addition

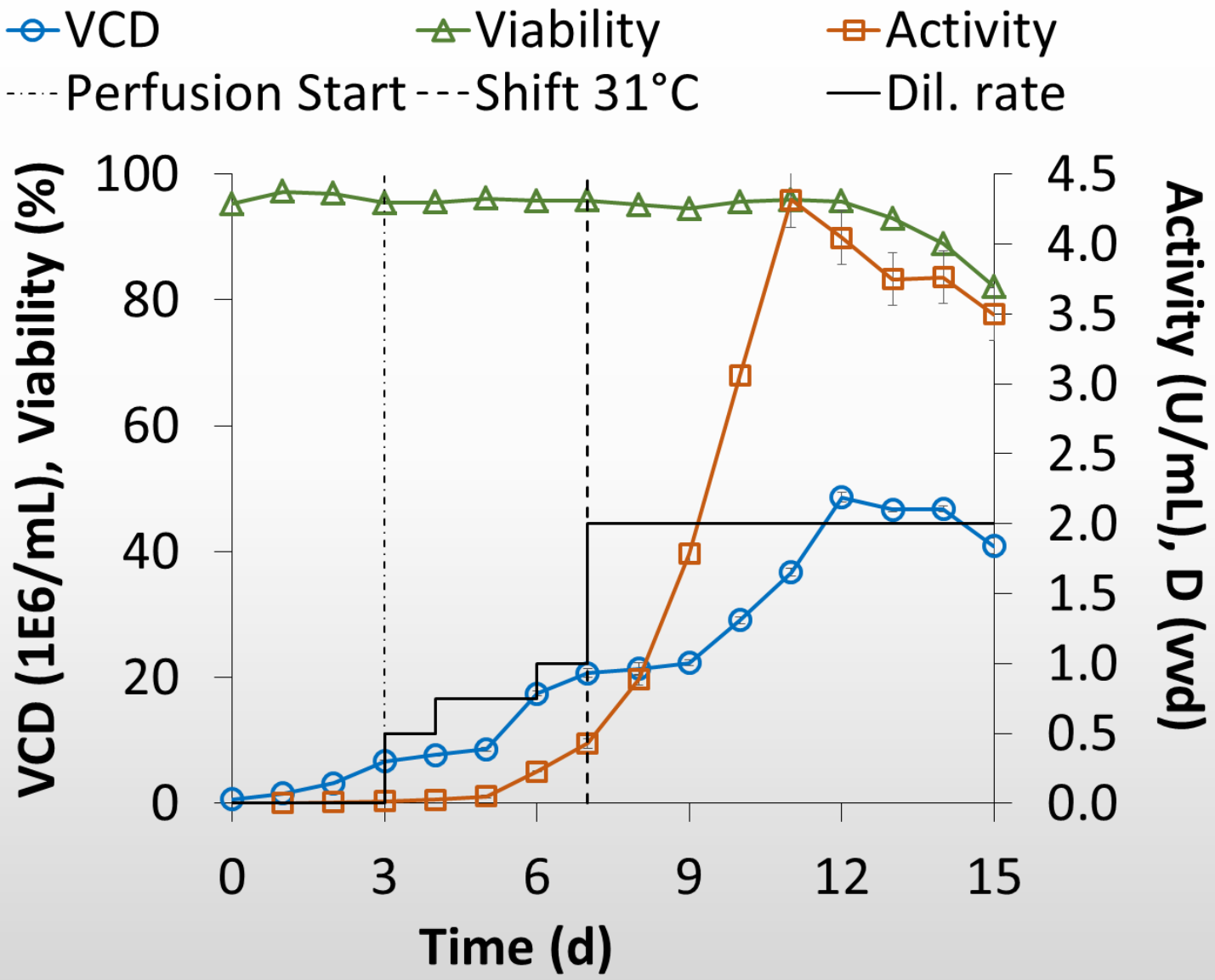
- Separate DOEs (2^2) for CHO-GBA-36K and CHO-GBA-65P clones
- spinner flasks in batch mode
- customized CD, ADCF medium (TC-LECC, Xell AG)



- Low temperature (31°C): beneficial for both clones
- Valeric acid supplementation: clone dependent effects
- Maximum q_p: CHO-GBA-65P, 58.4 nU/cell/d
  - ✓ 4.2 fold higher than control at 37°C
  - ✓ 2.7 fold higher than maximum for 36K clone

Biphasic perfusion

- CHO-GBA-65P clone
- Stirred-tank bioreactor with inclined settler
- Perfusion start on day 3
- Shift to 31°C on day 7



- Enzyme activity
  - ✓ 9.5x higher than batch at 31°C
  - ✓ 22x higher than batch at 37°C
- Perfusion process at low T: higher volumetric productivity & higher titer ⇨ good for DSP

THANKS!

DBE
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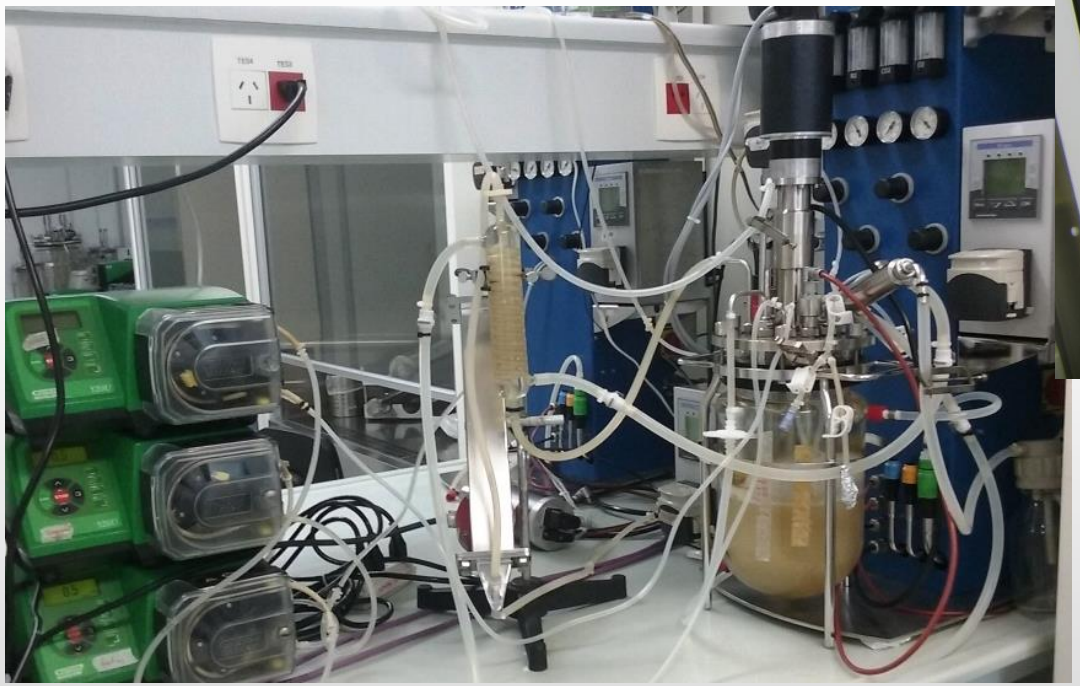

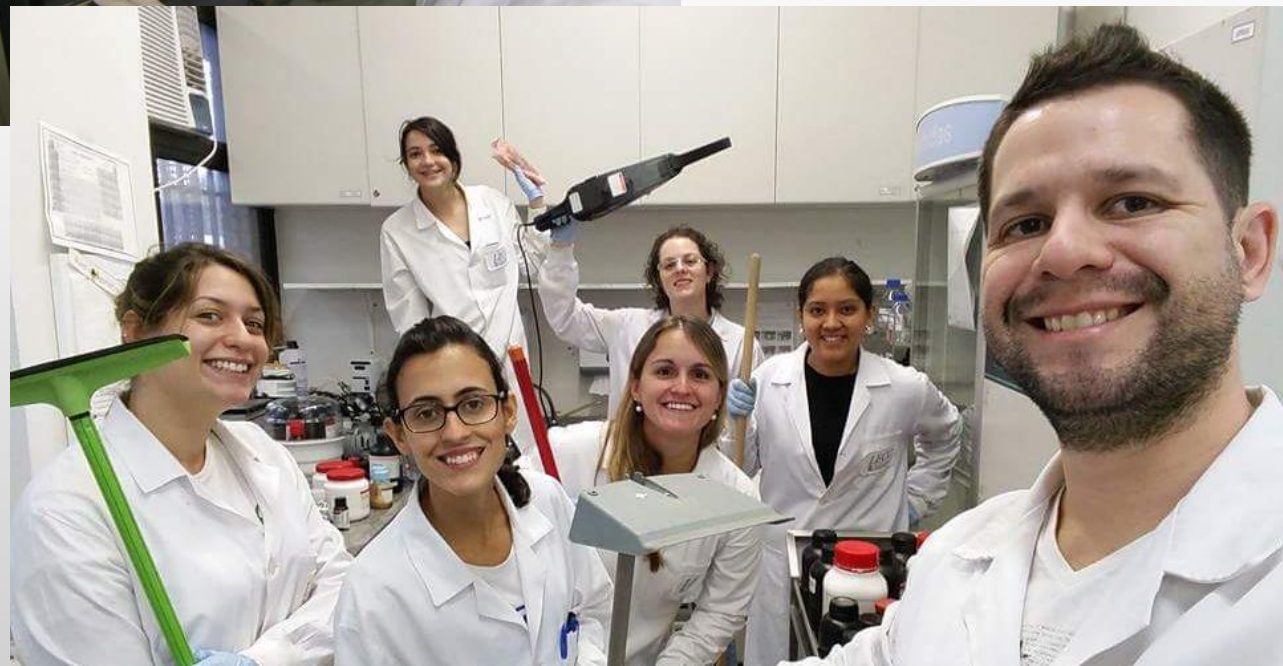

Financial support from CNPq, Capes, FAPERJ,
Santander Iberoamerican scholarship