CELL CULTURE AND SOCIAL ENGINEERING

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My work in cell culture justifying this CCE Award was only possible due to very strong backing from CCE pioneers as well as students, in particular from Universidade Nova de Lisboa, that made the dream of building iBET a reality. Mentored by experts and strengthened by excellent Ph.D. students, risk taking in cell process development of newer modalities paid off handsomely!

From iBET's creation (1988), process development and product quality of monoclonal antibodies was researched in partnership with ETH, GBF and CAMR. In the mid-nineties, realizing how many resources were being invested in CHO Mab's and how poorly funded we were, iBET started work on viruses for both vaccines and gene therapy: adenovirus, initially for veterinary vaccines (CIRAD and Pirbright), retrovirus for gene therapy (GBF and Genethon) and insect cells as tools, also for VLP's (LSHTM and CNRS). This permitted my Lab to carry out the first perfusion bioreaction for retrovirus, in the late nineties, opening up our search for development of continuous unit operations, for example, two column simulated moving bed chromatography. In the last decade we reached continuous integrated processes for AdV (now specially targeting oncolytic applications), AAV, and lenti-. This is an area of excellence at iBET, as also constitutive cell lines and affinity processes are being researched.

Then Paula Alves, a Ph.D. student who became iBET's CEO over ten years ago, invented a tubular perfusion bioreactor fitting inside a NMR magnet to test brain metabolic events through manipulation of neuron, astrocytes and glial cell aggregates. Twenty years later, iBET has a 3D complex cell culture track record of excellence in brain, liver and heart, including immune cells to check viral vectors immune responses, or sporozoites in liver to test for malaria drugs. Cancer cell models using human cells have been mastered for ten years.

iBET dived into hESC with Cellartis in 2005. Earlier knowledge on cell aggregate manipulation and microcarriers (for Vero cell-based vaccines) allowed us to expand and differentiate hESC, later also iPSCS. Ten years later we showed continuous integrated processes for iPSC and MSCS were possible, making cell therapy development and understanding another area of excellence.

As process proficiency in cell and gene therapy and process development matured at iBET, "tool provider" companies strengthened partnerships with us. For example, a prototype experimentally designed at iBET was built at Sartorius for the first membrane chromatography process for enveloped virus in 2007. Cytiva (then GE Healthcare) produced a uniformly sized batch of Captocore beads allowing us to purify iPSCS and MSC in expanded bed, flow through, chromatographic mode, in 2014. Ultimately our pursuit of affinity purification beyond MAbs constituted the basis for purifying low yield, complex glycoconjugate vaccines from GSK (Sienna) with nanofitins from Affilogic and eshmuno resins from Merck Life Sciences, simplifying the process, boosting yields and reducing costs (recognized as a success story by the funders of the DiViNe project, the Eur. Commission).

Mathematical modelling constitutes the backbone of process development at iBET, not only for cell cultures. In the late nineties iBET developed a process based on Pichia pastoris to produce FAbs; the methanol induction probes and control equations thus developed were cleared for publication by Berlex, the sponsor, in the early 2000's. The hybrid models thus introduced where later optimized for Merck & Co's Glycofi MAb's and consolidated iBET as a key player in P. pastoris platforms, nowadays gaining preference for microbially expressed biopharmaceuticals.

The startups for whom iBET developed processes pushed us to expand into GMP production for early clinical trials. GenIBET Biopharmaceuticals, created in 2007, had Novartis Vaccines Institute for Global Health, Sienna, as a launching partner for a Typhoid vaccine candidate, now being produced in India. Initially working with European customers, GenIBET got a major boost in activity and enlarged competences when American style driven companies became customers: Moderna (2014-2018), Seres (2015-) or Turnstone (2018-). (GenIBET was sold to Recipharm in January 2022)

All this fortunate “social engineering” was further reinforced by contributing to the European Society for Animal Cell Technology (ESACT) and various series of conferences from Engineering Conference International (ECI). Cherished cooperations outside the rich northern hemisphere - Universidade Federal do Rio de Janeiro and Instituto Butantan (Brazil), National Veterinary Institute (Debre Zeit, Ethiopia), Inst. Pasteur de Tunis and Universidade Nacional Autonoma de Mexico, Cuernavaca – yielded long term friendships

As iBET keeps tackling challenging problems, with a frugal search for solutions, driven by excellent and committed researchers, I am very confident it will continue contributing to biotechnology solving human health, food and environmental acute needs.