

Global 3R approach and bioreactors in biomedical research

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Biomedical research needs preclinical models able to discriminate among the organs crosstalk and to distinguish mechanisms of action. A global 3Rs approach in our works led to important observations and technological spillovers, ensuring animals' welfare and their partial Replacement in certain experimental steps. In the last decade, our group applied a global 3R approach in several preclinical models, Refining techniques, Reducing the number of animals and partially Replacing some *in vivo* procedures by using bioreactors in a millifluidic system. The published results showed better analgesic strategies, described animals' behaviors associated with specific *in vivo* procedures, and highlighted correlations among brown adipose

tissue temperature, stress, weight, neuroinflammation and handling. Working on Refinement, the issue of finding a model to investigate the organ crosstalks alteration activated by distress arose. Animals are too complex and cells in a petri dish too simple. Bioreactors allowed to explore crosstalks in a way impossible with classic *in vivo/in vitro* models. In our 2022-awarded work on PlosOne 2020 (www.aaalac.org/awards/global-3rs-winners) we assessed a simplified model of nervous-cardiovascular crosstalk in bioreactors, finding that coronary-artery and neuroblastoma cells connected under flow conditions started a dialogue triggering the activation of PKC β II/HuR/VEGF pathway after angiotensin II treatment. This activation was not present when cells were subjected to flow and treatment, but not connected with each other. Bioreactors will be used in our 2023-2024 CAAT granted project (<https://caat.jhsph.edu/programs/grants/>), which will deal to cardiovascular issues not addressable with current *in vivo/in vitro* models. Bioreactors appears a promising strategy to test new therapies without the use of animals.

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