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AGENT-BASED GENETIC MULTICELLULAR 3D MODELLING OF STEM-CELL SPHEROIDS (GENESPHERE)

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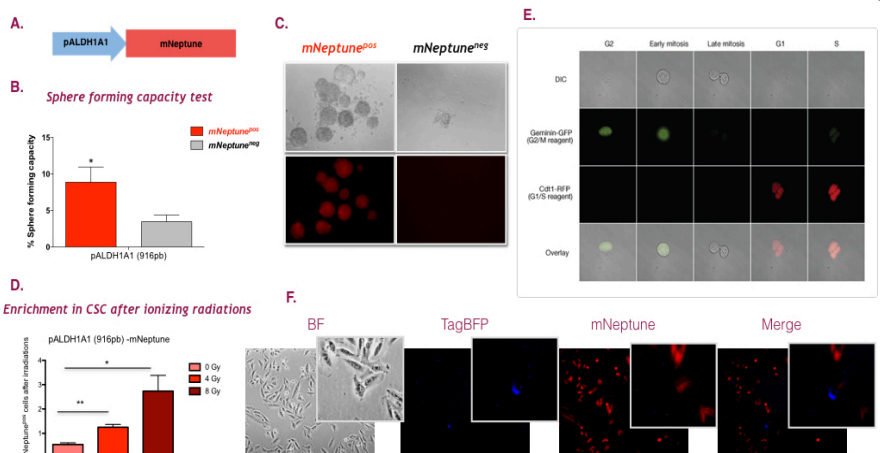
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COULD X-ray IRRADIATED BREAST-CANCER CELLS REPROGRAM INTO CANCER-STEM-CELLS ?

The main objective of GENESPHERE is to produce a model capable of testing the hypothesis of radiation-induced breast cancer stem cells.

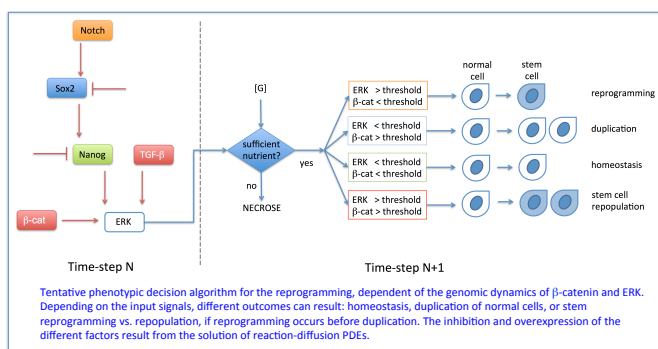
In recent experiments, we observed CSC-specific markers to appear in irradiated non-tumorigenic cells (T47D, MCF-7, MDA-MB-231 and SUM159-PT), either isolated, or in presence of pre-existing breast-CSCs. We characterized the up-regulation of about 10 different genes, among which key elements of the *Notch* pathway; it was shown, e.g., that simultaneous down-regulation of Sox2 and Nanog significantly reduced the generation of new breast-CSCs, contrary to down-regulation of either one alone; also, down-regulation of *Notch* receptors reduced the ability to form spheroids and radiation-induced reprogramming.



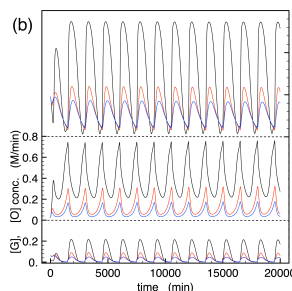
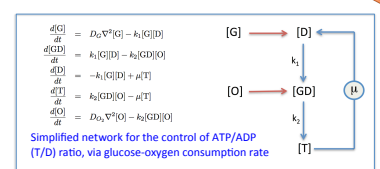
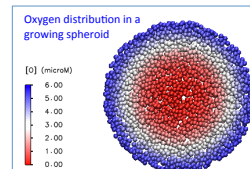
Growth of 3D multicellular spheroids is an important assay in CSC studies

GENESPHERE: AN AGENT-BASED MODEL

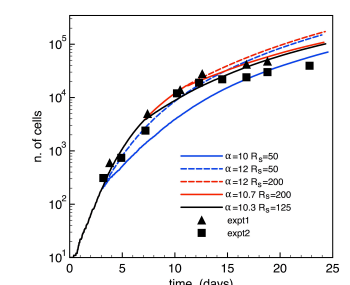
The **Agent-Based Model** describes motile cells in a 3D network of Voronoi polyhedra. Each cell-agent has: a local phase clock; duplication with genetic inheritance; normal, stem, or various cancer-cell phenotype; diffusion of oxygen, nutrients, or other chemicals; a basic version of the glycolysis cycle, with the ATP demand setting the level of glucose/oxygen consumption. Cells can absorb radiation/chemical damage, described by a Markov chain, with individual cell-repair mechanisms. The next level of enrichment of the model is the inclusion of a **cell systemic network**, with a whole new sets of cell markers describing activation/repression of different factors that could characterize the CSC and radiation-induced CSC populations, by means of PDE-based kinetic modeling.



SOME RECENT RESULTS



Single-cell-based modeling of periodic glucose-oxygen supply at constant ATP consumption rate (μ). Black/red/blue=9/18/36 mM [glucose]



Long-term 3D spheroid growth ABM simulation including necrosis, quiescence and cell shedding [Exp. data from Y. Jiang et al. Biophys. J. 89, 3884 (2005)]

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