CELLULAR BIONICS TO INTERFACE LIVING AND NON-LIVING

THE NEXT GENERATION OF PROGRAMMABLE CANCER THERAPIES

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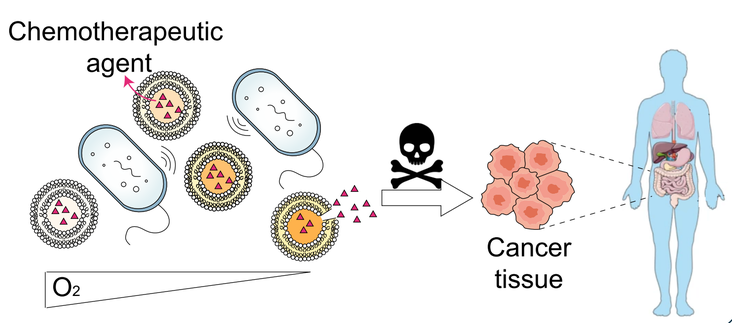
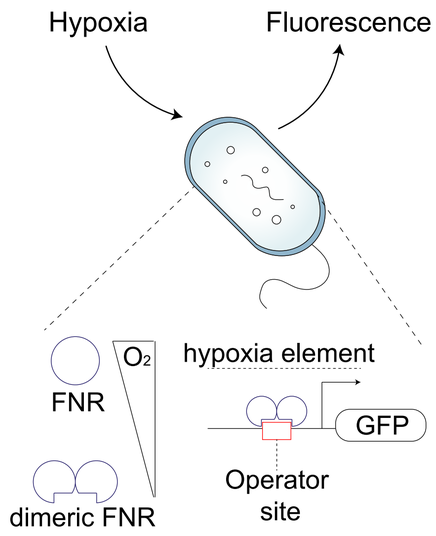
The Grand Challenge - Cellular Bionics to Fight Cancer

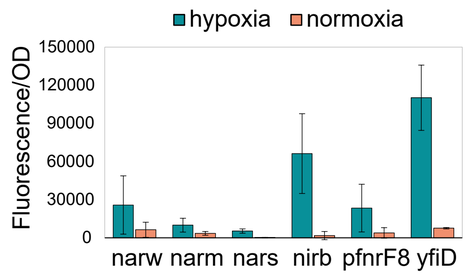
One of the major challenges in modern medicine is ensuring drugs specifically target diseased cancer cells. The aim of this work is to build cellular bionic systems that can recognise cancer cells and kill them too. **We are working to interface living bacteria and non-living artificial cells to build a biohybrid that can respond to the low oxygen environment present in tumours by releasing chemotherapeutic agents.** This and similar cellular bionics platforms will pave the way for customisable synergies between living and artificial cells triggered by chemical and physical stimuli, unlocking a whole new suite of clinical and industrial innovations.



Engineering bacteria to sense hypoxia

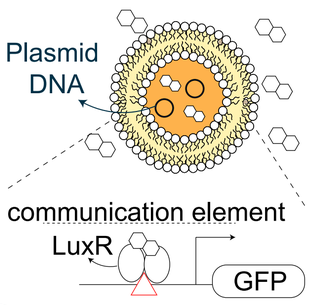
To build biohybrids we first need to program the living component. **We genetically engineered bacteria to sense hypoxia and respond by expressing a fluorescence gene (GFP).** We developed a suite of hypoxia-responsive elements activated by an oxygen-sensitive regulator (FNR). In this way, bacterial fluorescence can be used as an indicator of hypoxic environments.

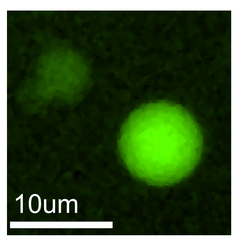


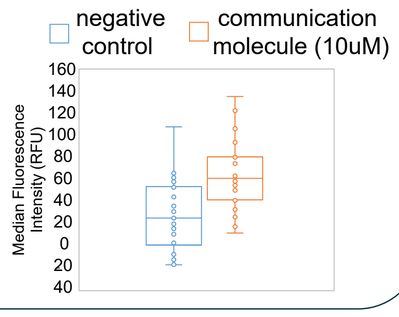


Building programmable artificial cells

To build the biohybrid, we need to plug in genetically-programmable artificial cells as non-living component. **We constructed programmable artificial cells capable of sensing the communication molecule and responding by expressing a fluorescence gene.** We proved that the communication molecule is able to cross the membrane of artificial cells and induce gene expression from encapsulated DNA. We have now validated all the modules needed to assemble the full biohybrid system.



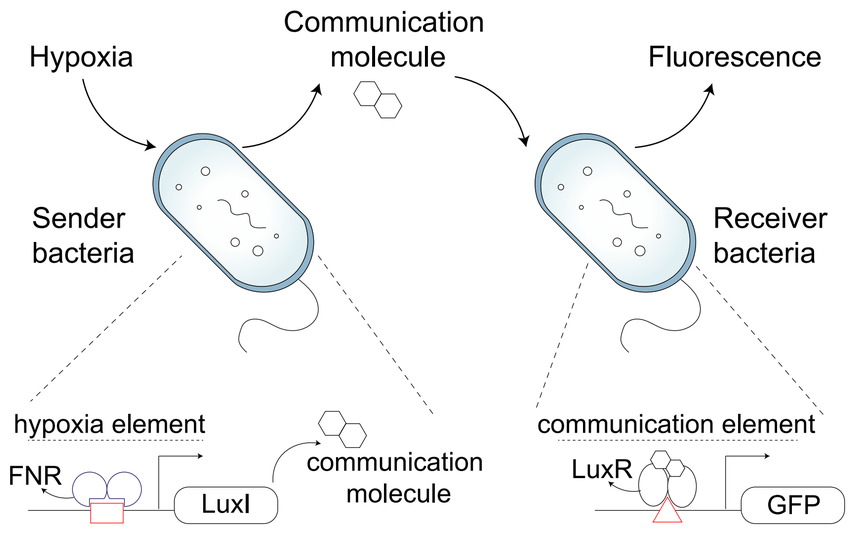




Figuring out the communication route

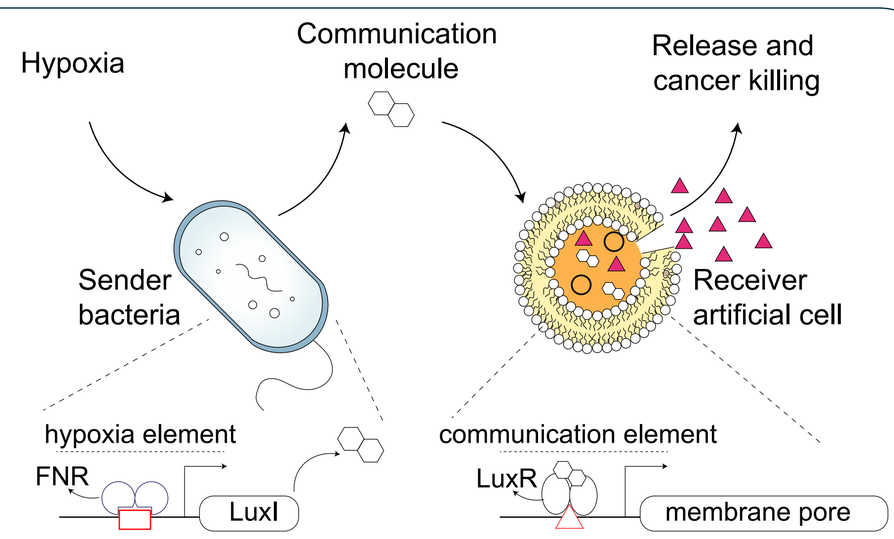
To function in a biohybrid system, our engineered bacteria must communicate with non-living artificial cells. To achieve this, we first engineered a one-way communication route between two bacteria populations, with the aim of translating it to a biohybrid system once established.

We engineered (1) a first population of “sender” bacteria to produce a communication molecule only in hypoxic environments, and (2) a second population of “receiver” bacteria to pick up the communication molecule and respond to it by expressing a fluorescence gene. This way, we can use the fluorescence from the receiver bacteria as a proxy of successful hypoxia-dependent communication. We show that the fluorescence of receiver bacteria increases when in contact with the growth media of sender bacteria cultured in hypoxic environments. **We proved that our communication molecule enables efficient one-way hypoxia-dependent communication between two separate bacteria populations.**



Next-steps - closing the loop

The final step will be to piece all the modules together to **create the first biohybrid capable of sensing oxygen depletion in the tumour microenvironment and releasing chemotherapeutic agents directly on cancer site**. So far, we have engineered bacteria that respond to hypoxia by producing a communication molecule, which artificial cells can internalise and use to drive custom gene expression programs. In the next months, we will hybridise our engineered bacteria with artificial cells containing a chemotherapeutic agent and programmed to release it only when encountering hypoxia at the tumour site, paving the way for the use of biohybrids in medical applications.



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