LCPO AND ANR MAVERICK PRESENT

CELL NANOBLENDERS

TO TREAT CANCERS WHILE WEAKENING PATIENTS AS LITTLE AS POSSIBLE, WE ARE LOOKING FOR WAYS TO ATTACK SICK CELLS FROM UP CLOSE.

DIANA KAZARYAN

IMAGINE AN OBJECT THAT WOULD BE:

- MICROSCOPIC: CARRIED TO THE TUMOR BY THE BLOODFLOW
- SNEAKY: INVISIBLE TO THE IMMUNE SYSTEM

AND CONTROLLABLE: ONCE INSIDE A SICK CELL, IT CAN BE ORDERED TO KILL IT:

SICK CELL

YUM!

KILL

BOOM!

CLIC

KILL

ARGH!

WITH PROJECT MAVERICK, OUR ATTACK STRATEGY IS TO SHRED THE MEMBRANES IN THE CELL:

THE CELL WALL ITSELF, WHICH SEPARATES THE CELL FROM THE REST OF THE BODY

AND ALSO THE MEMBRANE OF LYSOSOMES: SMALL POCKETS FULL OF ENZYMES, THAT THE CELL USES TO DIGEST PROTEINS

NOM!

NOM!

NOM!

SNIP!

SO, HERE, WE RIP IT OPEN A BIT...

ET RESNIP!!

NOM!

NOM!

NOM!

AND THERE, IT SELF-DIGESTS!

THAT CELL'S QUITE DONE FOR.

AND AS A REMOTE CONTROL, WE WANT TO USE A ROTATING MAGNETIC FIELD: NON-INVASIVE, NOR HARMFUL TO HEALTHY CELLS.

FIELD GENERATOR

CANCER GROWTH, FULL OF OUR MYSTERY OBJECT...

... ELONGATED NANO-OBJECTS, SPINNING IN THE MAGNETIC FIELD LIKE TINY BLENDERS INSIDE THE CELL:

TCHAC!

A WELL-SHREDDED MEMBRANE!

TO SHRED MEMBRANES EFFICIENTLY WITH A ROTATING OBJECT WITHOUT NEEDING A STRONG FIELD, WE CAN ACT ON TWO PARAMETERS:

- THE MORE ELONGATED THE OBJECT, THE MORE LEVERAGE IT HAS TO PUSH ON THE MEMBRANE:

HUFF!

OH YEAH, THAT'S EASIER!

NO NEED TO TRY HARD!

- THE MORE MAGNETIC THE OBJECT, THE STRONGER THE PUSH:

A FEW MAGNETIC NANOPARTICLES

I FEEL A BIT WEAK...

A LOT OF MAGNETIC NANOPARTICLES

TAKE THAT, MEMBRANE!

TO MAKE SUCH OBJECTS, WE'LL PROCEED IN THREE STEPS.

1

2

3

STEP 1: CHEMICAL SYNTHESIS

WE CREATE SOFT AND HOLLOW MICROSPHERES, OR "VESICLES":

A FLEXIBLE MEMBRANE...

...LOADED WITH MAGNETIC NANOPARTICLES...

CROSS-SECTION VIEW

DIAMETER: 50 TO 100 NANOMETERS (10 TO 1000 TIMES SMALLER THAN A CELL)

... AND MADE OF MOLECULES WITH DESIRED PROPERTIES, USING A CUSTOM RECIPE.

STEP 2: DEFORMATION UNDER MAGNETIC FIELD

S Z

THE NANOPARTICLES ALIGN WITH THE DIRECTION OF THE FIELD, PULLING THE SOFT MEMBRANE ALONG WITH THEM...

STEP 3: STIFFENING IN UV LIGHT

S Z

A NICE ELONGATED POTATO, FOREVER!

UV LIGHT TRIGGERS A CHEMICAL REACTION INSIDE THE MEMBRANE: IT BECOMES STIFF, AND WILL KEEP ITS SHAPE OUTSIDE THE FIELD.

AND HERE IS A NANOBLENDER!

FINDING A "CUSTOM RECIPE" TO MAKE VESICLES THAT WOULD SUIT OUR NEEDS IS A BIG PART OF MY PHD WORK!

FIRST, NOT ALL MOLECULES CAN FORM THAT KIND OF STRUCTURE.

WANTED

SOFT & HOLLOW VESICLE

$ GOOD REWARD $

WHAT'S THAT?

NEVER SEEN ANYTHING LIKE IT!

YOU NEED "POLYMER" MOLECULES: LONG CHAINS OF SMALLER MOLECULAR UNITS, LINKED TOGETHER LIKE A PEARL NECKLACE:

"MONOMER": THE SMALL UNIT

+ ENERGY, CATALYST, ETC. ...

POLYMERIZATION REACTION

"POLYMER": THE MOLECULAR EQUIVALENT OF A NOODLE

AND EVEN SPECIFIC POLYMERS, MADE OF PARTS WITH DIFFERENT CHEMICAL AFFINITIES, TIED TOGETHER:

HYDROPHILIC PART

HYDROPHOBIC PART

LET'S GO FOR A SWIM?

LET'S NOT GO FOR A SWIM!

...

AND WE'D CALL THAT "FRANKENSTEIN'S POLYMERS"

ABSOLUTELY NOT! "BLOCK COPOLYMER", IT'S MORE ACCURATE.

BECAUSE IT'S MADE OF BLOCKS.

SEE?

IN WATER, THESE MOLECULES SPONTANEOUSLY ASSEMBLE INTO STRUCTURES THAT GROUP THE HYDROPHOBIC BLOCKS TOGETHER.

WE WANT TO DEMIX, LIKE OIL IN WATER...

BUT WE'RE TIED TOGETHER!

WATER

GEOMETRICAL SOLUTION: CHAINS PLACED IN A DOUBLE LAYER

NICELY PROTECTED!

DEPENDING ON THE NATURE AND PROPORTION OF THE BLOCKS IN THE CHAIN, COPOLYMERS FIND DIFFERENT SOLUTIONS:

PROPORTION OF ↗

WE CAN GET:

FILLED SPHERES, OR "MICELLES"

"WORMS" (CYLINDRICAL MICELLES)

HOLLOW SPHERES, THE VESICLES

WE WANT THAT!

WHY SPECIFICALLY VESICLES, AND NOT MICELLES?

WELL, IT'S EASIER TO SQUISH A SOFT, THIN MEMBRANE THAN A PACKED SPHERE...

AND A HOLLOW OBJECT COULD CARRY ALL SORTS OF USEFUL THINGS FOR FUTURE PURPOSES

IN PARTICULAR, THERAPEUTIC MOLECULES! (BUT THAT'D BE FOR LATER)

THESE POLYMER VESICLES ARE CALLED POLYMERSOMES

FROM POLYMER (YES)

AND SÔMA, "BODY" IN GREEK

AND HAVE BEEN DEVELOPPED SINCE THE MID 1990's FOR A VARIETY OF USES IN NANOMEDICINE.

I'M AN ARTIFICIAL CELL!

I CARRY DRUGS!

I CAN HEAT LOCALLY, TO KILL CANCER CELLS!

THEIR BIG ADVANTAGE IS THAT BY CHOOSING ~~ AND ~~ CAREFULLY, WE CAN GIVE THEM CUSTOM PROPERTIES, FOR EACH USE.

HERE, WE NEED:

CONSTRAINT 1 DIFFICULTY ★

MUST BE:

(1) INVISIBLE TO THE IMMUNE SYSTEM

(2) "BOUNCY"

POK

SO AS NOT TO CLOG THE BLOOD VESSELS!

CONSTRAINT 2 DIFFICULTY ★★★

MUST BE:

A SOFT ELASTOMER

THAT REACTS UNDER UV LIGHT TO FORM A STIFF NETWORK OF TIGHT LINKS

CONSTRAINT 3 DIFFICULTY ★★

THE MAGNETIC NANOPARTICLES MUST FIT INSIDE THE MEMBRANE

HYDROPHOBIC SURFACE TREATMENT

AND OF COURSE, IT MUST BE BIOCOMPATIBLE!

WITHOUT FURTHER ADO, HERE IS A RECIPE I CREATED DURING MY PHD:

ON THE OUTSIDE, WE HAVE PEG: A POLYMERSOME VETERAN, IT'S BEEN EVERYWHERE, DONE EVERYTHING

INSIDE THE MEMBRANE, A NEWCOMER: A BRUSH COPOLYMER, WITH SIDE BRANCHES THAT WILL REACT IN UV LIGHT AND MAKE A TIGHT NETWORK!

INTERLUDE: A BIT OF CHEMICAL COOKING

HOW DO WE GO FROM:

PEG, COMMERCIALLY AVAILABLE

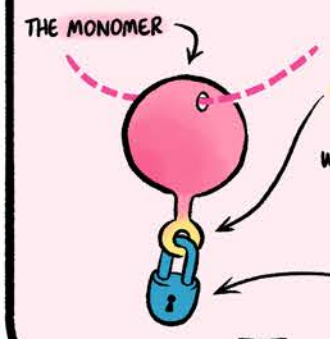
LOTS OF DIFFERENT MOLECULES

TO:

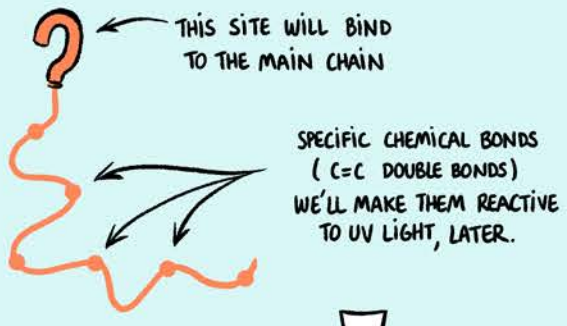
LOVELY MAGNETIC POLYMERSOMES ?

FIRST, LET'S MAKE THE BRUSH COPOLYMER :

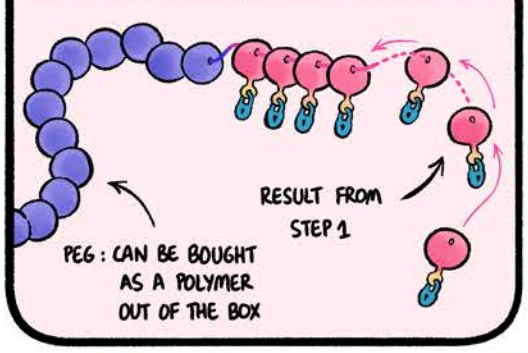
1 MAKING THE BUILDING BLOCK FOR THE MAIN CHAIN



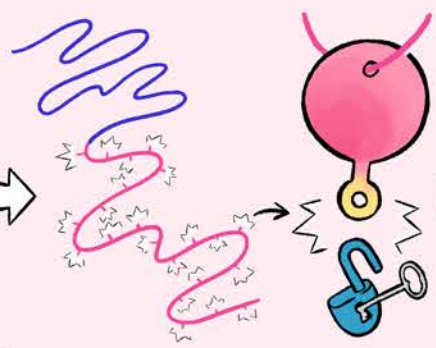
2 MAKING THE SIDE-CHAINS (SEPARATELY)



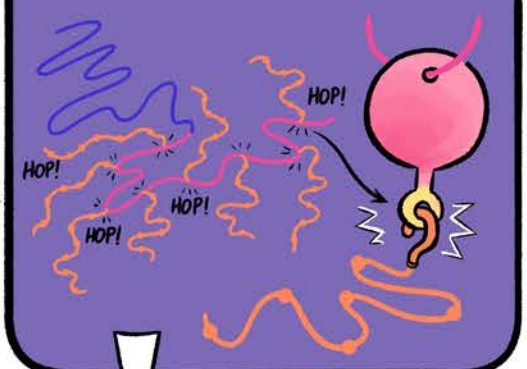
3 ASSEMBLING THE MAIN CHAIN (JUST THE BACKBONE, NO BRANCHES YET)



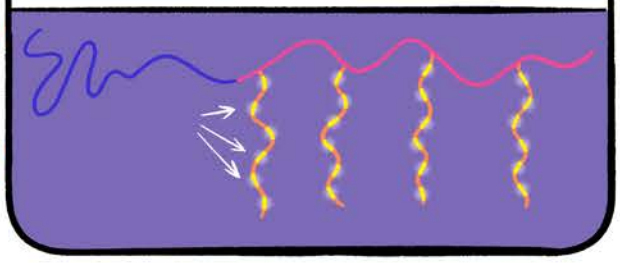
4 DEPROTECTING THE BINDING SITES...

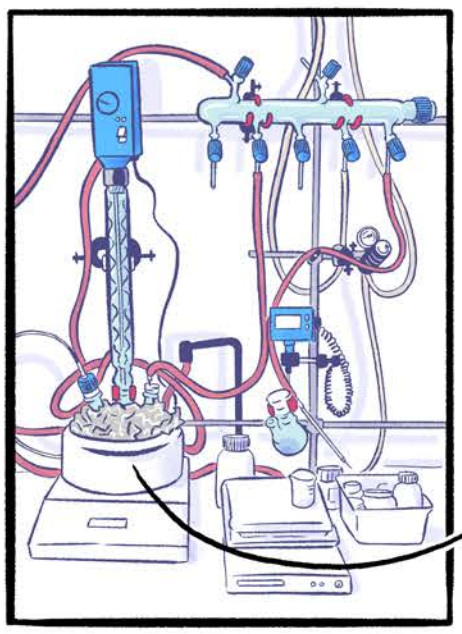


...THEN 5: ATTACHING THE SIDE CHAINS

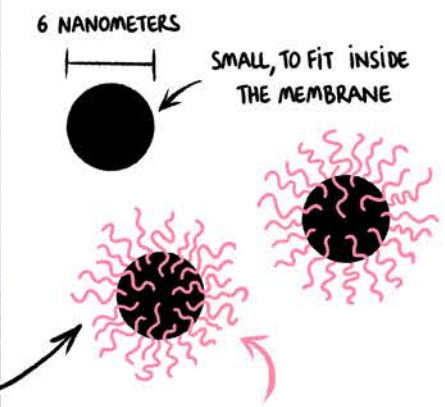


AND LASTLY, 6: MODIFYING THE C=C DOUBLE BONDS SO THEY'LL REACT TO UV LIGHT IN THE FINAL STEP

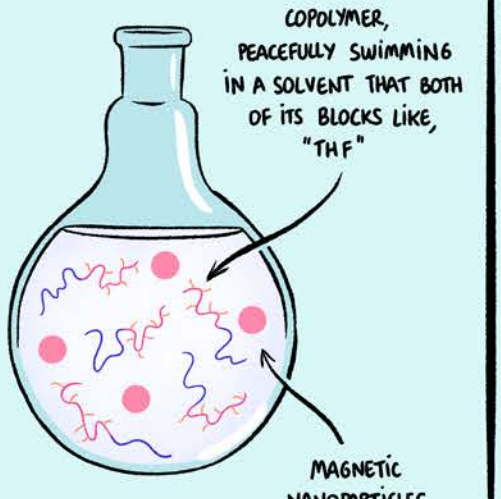


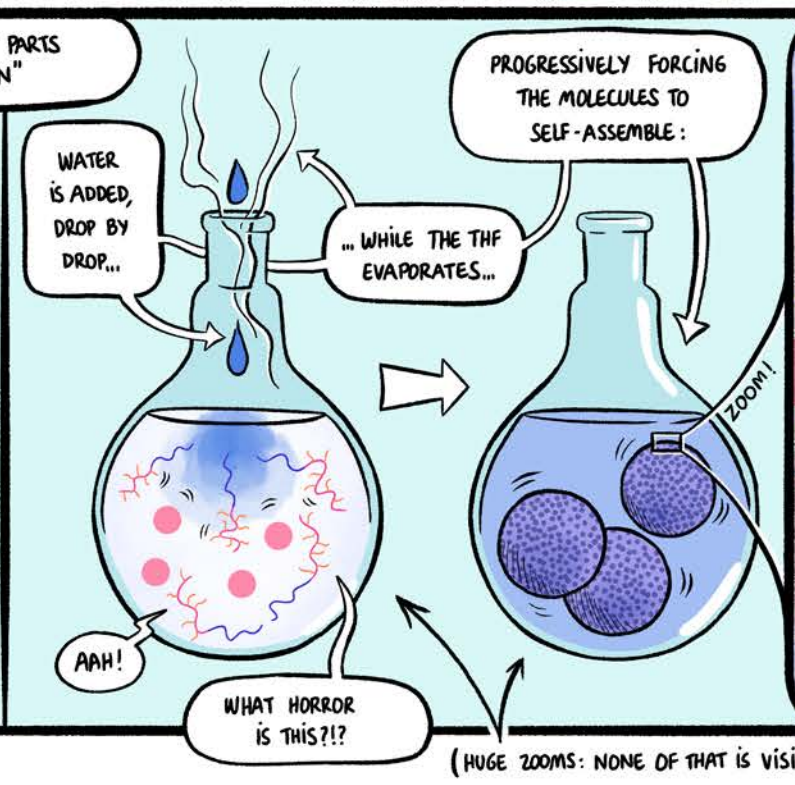


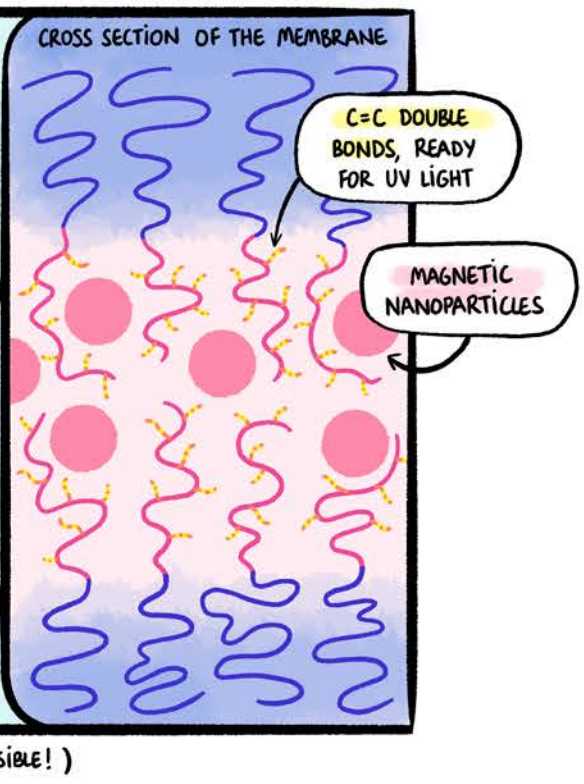
IN PARALLEL TO ALL THAT, WE HAVE TO SYNTHESIZE THE MAGNETIC NANOPARTICLES, AND MAKE THEM DISPERSIBLE IN THE MEMBRANE OF OUR FUTURE POLYMERSOME.



FINALLY, THE SELF-ASSEMBLY OF THESE DIFFERENT PARTS HAPPENS ALL TOGETHER, BY "NANOPRECIPITATION"







AND NOW, AFTER ALL THIS HARD WORK, IT'S TIME FOR A LITTLE UV SESSION...

ALLRIGHT!

WHERE DO I GO?

I'M READY!

WELL, RIGHT HERE, IN THIS SMALL TUBE!

POLYMERSOMES + INITIATOR SENSITIVE TO UV LIGHT, TO START THE CHEMICAL REACTION

WE BUILT THIS CHAMBER TO BE ABLE TO GENERATE A UNIFORM MAGNETIC FIELD.

MAGNETIC CHAMBER CUSTOM-MADE AT THE LAB (3D-PRINTED)

UNDER A MAGNETIC FIELD, THE NANOPARTICLES BEHAVE LIKE TINY MAGNETS, ALIGNED WITH THE FIELD:

S

N

REPULSION

ATTRACTION

IN A UNIFORM FIELD, THE MAGNETIC FORCES BETWEEN PARTICLES ARE DOMINANT:

SAME FIELD INTENSITY EVERYWHERE

THEY ALIGN INTO PARALLEL CHAINS,

AND THE POLYMERSOME STRETCHES, AS PLANNED

BUT IF THE FIELD INTENSITY IS NOT UNIFORM, THE PARTICLES WILL INSTEAD MOVE TO WHERE THE FIELD IS STRONGEST:

AS IF THERE WAS A BIG MAGNET

(WEAK FIELD HERE)

(STRONG FIELD HERE)

NOT VERY STRETCHED + MOVING = NOT AT ALL WHAT WE WANT!

FOR MAGNETS TO GENERATE A UNIFORM FIELD, THEY MUST BE ARRANGED IN A SPECIFIC WAY.

A SINGLE MAGNET:

(STRONG FIELD HERE)

(WEAK THERE)

HALBACH ARRAY ARRANGEMENT:

UNIFORM FIELD AT THE CENTER!

HERE, THE SAMPLE IS PLACED AT THE CENTER OF MAGNETS IN SUCH A CONFIGURATION

AND AN OPTICAL FIBER BRINGS THE UV LIGHT

UNDER UV LIGHT, THE SIDE BRANCHES OF THE POLYMER REACT, CREATING A DENSE NETWORK, AND THE MEMBRANE STIFFENS

IT WORKED!!

100nm

AFTER CHECKING CAREFULLY THAT WE DID CREATE ELONGATED OBJECTS...

TWO SERIES OF UV-EXPOSED POLYMERSOMES ARE COMPARED:

TEAM 1

WE'RE THE CONTROL GROUP!

- UV EXPOSURE: YES ✓
- UNDER MAGNETIC FIELD: NO ✗

TEAM 2

WE'RE THE FINAL GOAL!

- UV EXPOSURE: YES ✓
- UNDER MAGNETIC FIELD: YES ✓

... WE'RE NOW READY TO PASS THE BALL TO OUR BIOLOGIST COLLEAGUES, WHO WILL TEST THE POLYMERSOMES ON REAL TUMORS!

PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR

POLYMOWHAT NOW?

IS THAT A NEW CURE?

TO BE CONTINUED...

naïs COQ 2023