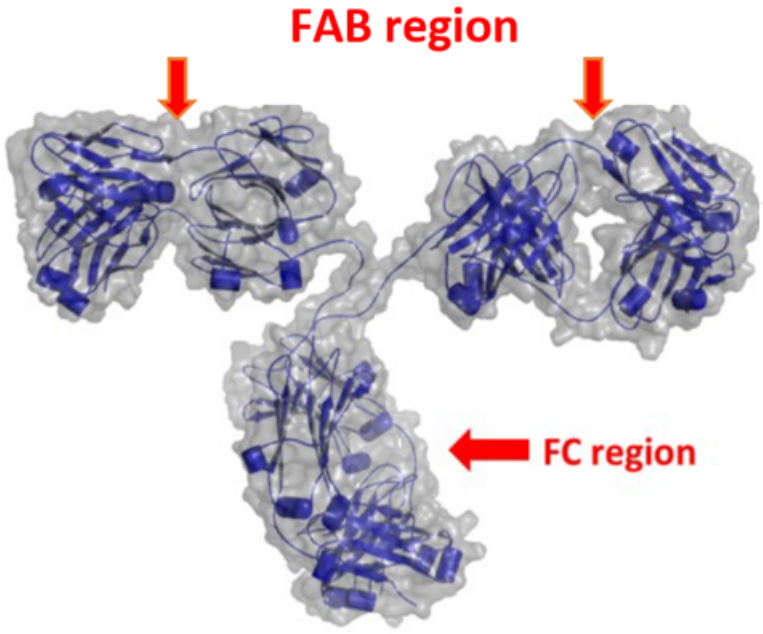
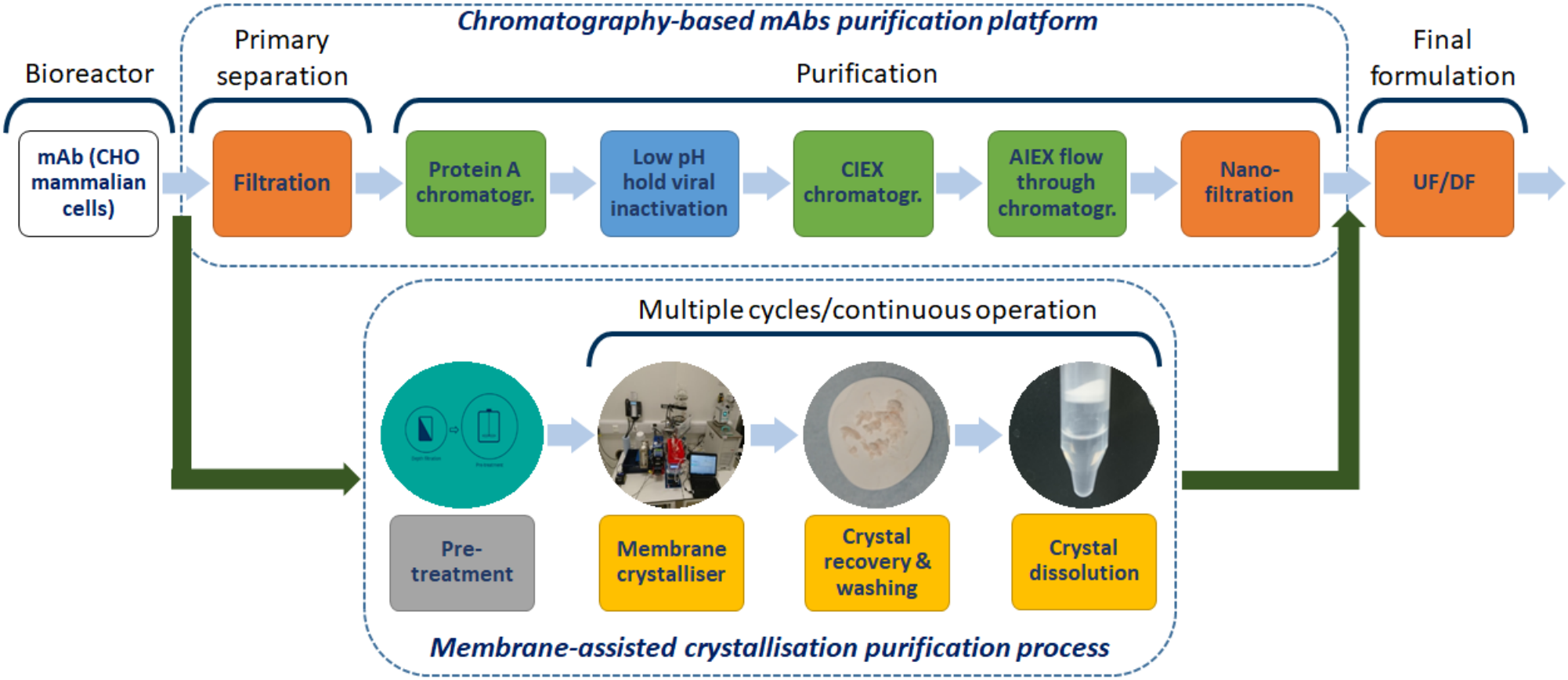
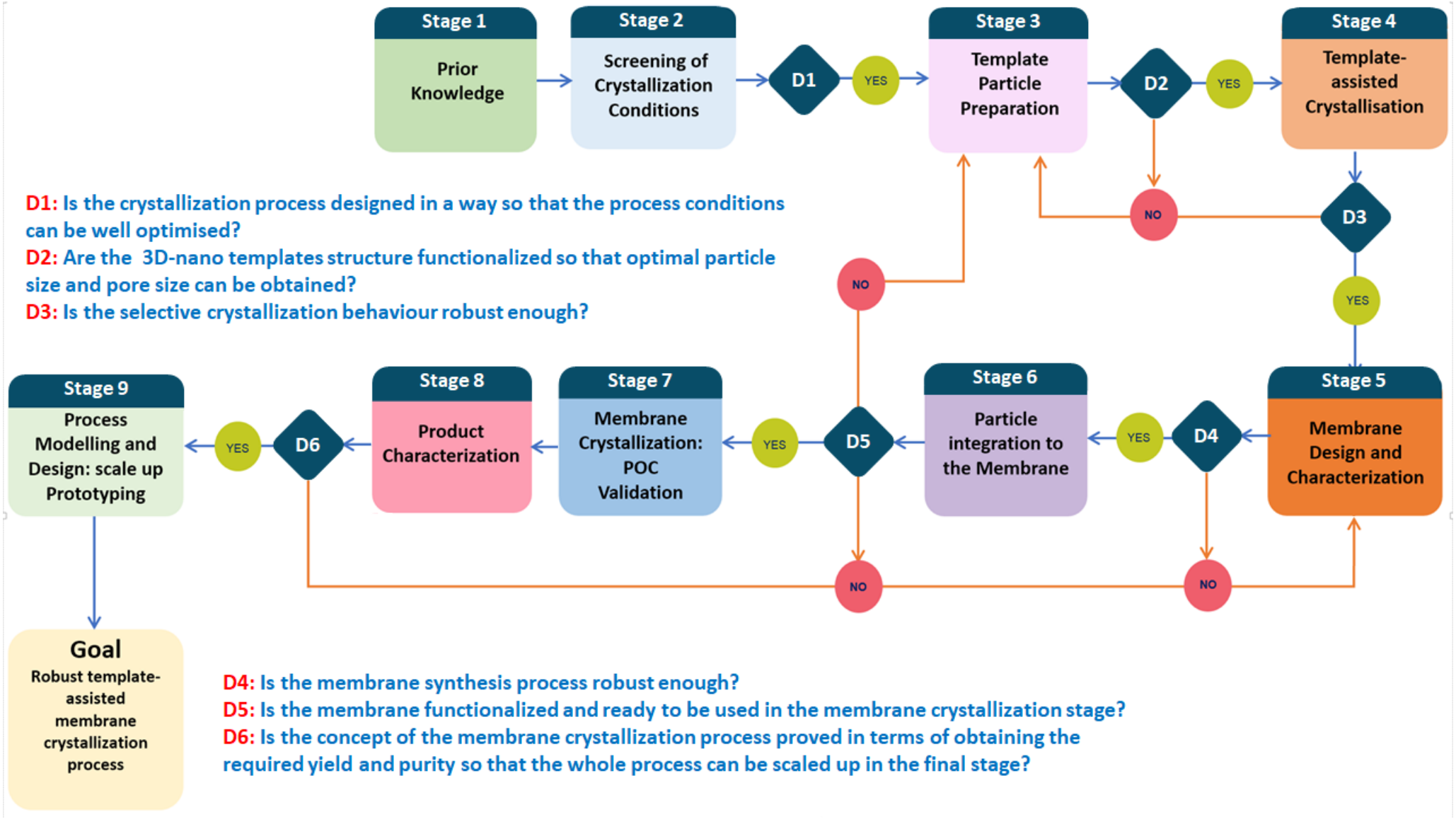
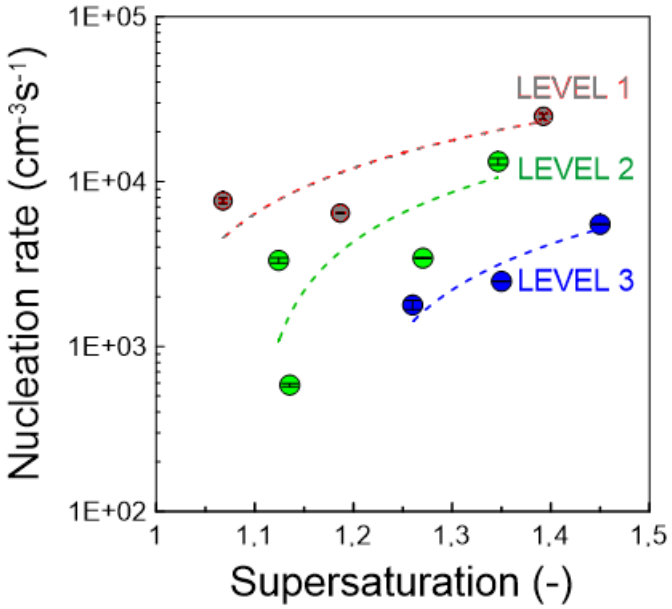
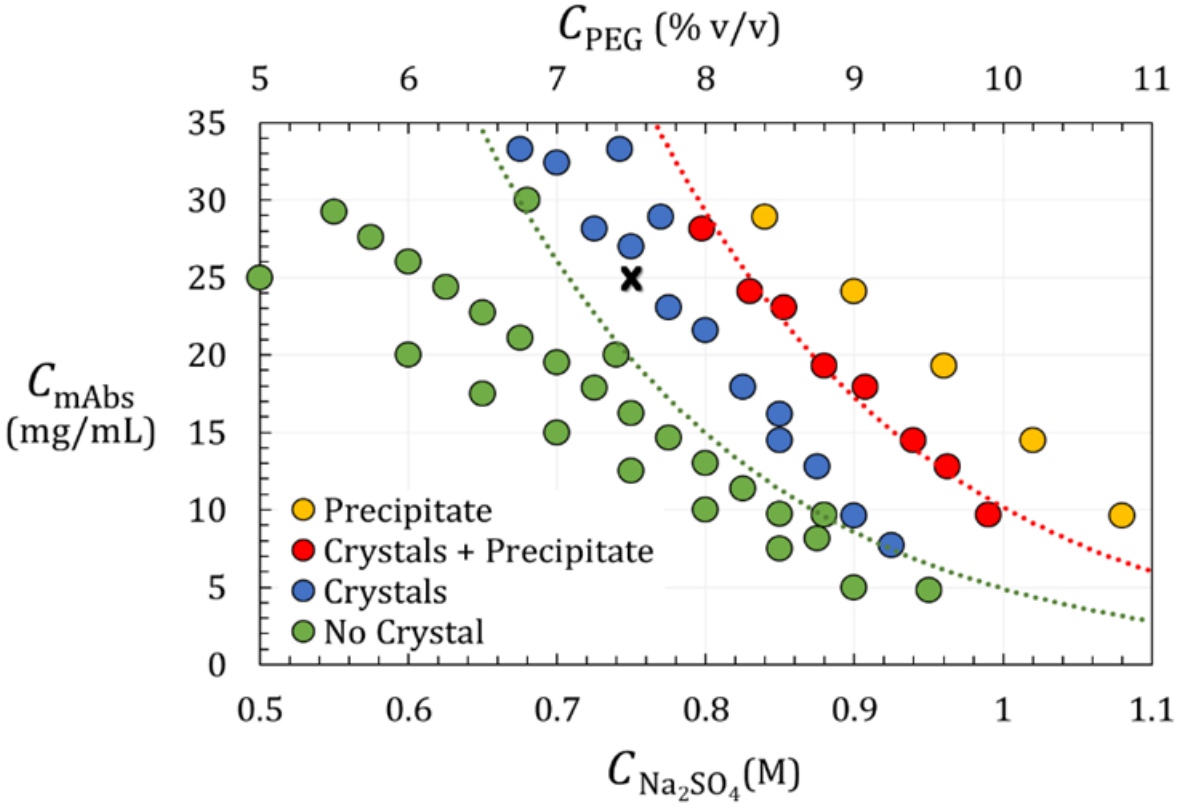
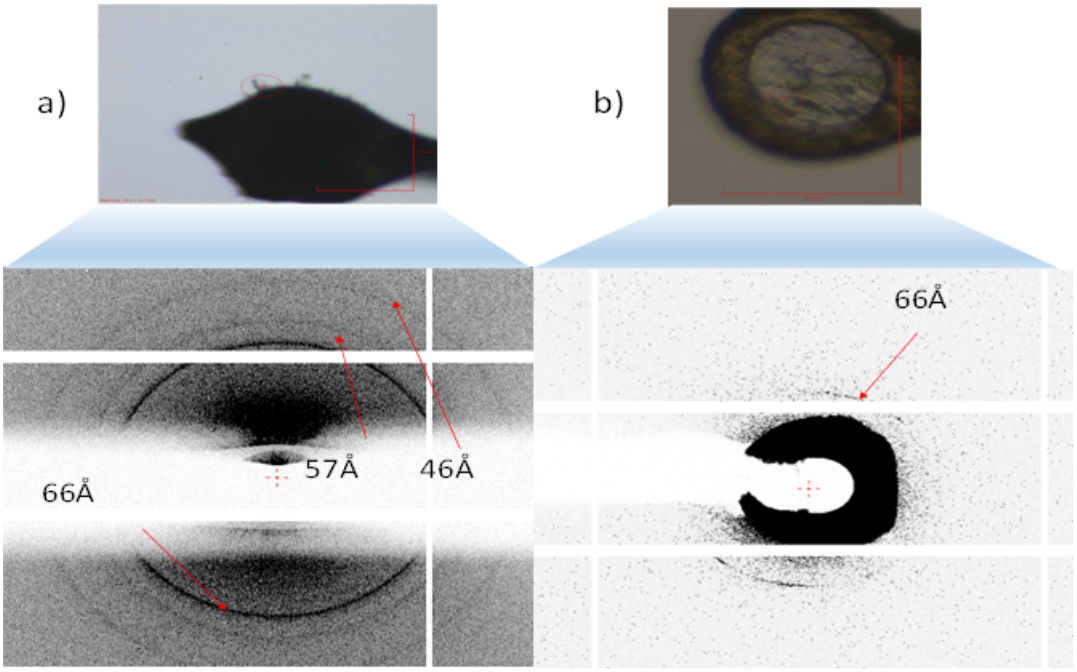

FAB region
FC region

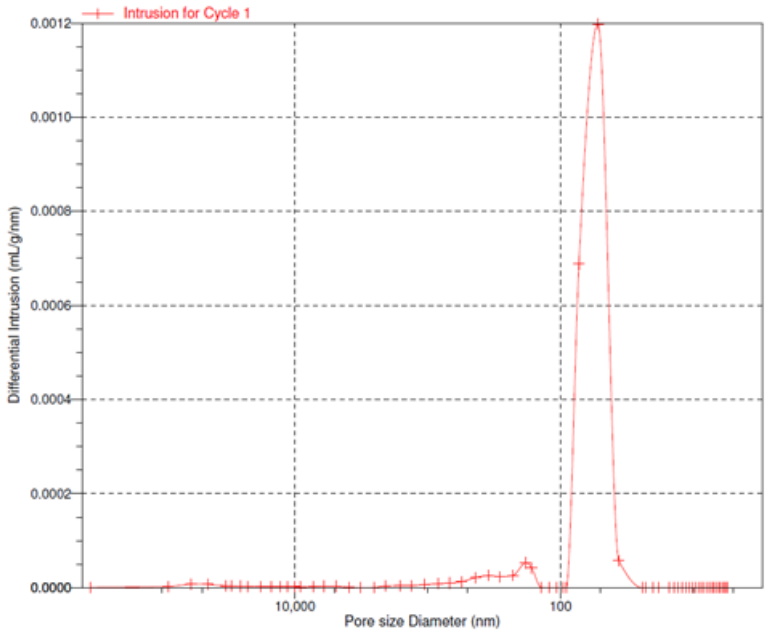

Chromatography-based mAbs purification platform
Bioreactor
Primary separation
Purification
Final formulation
mAb (CHO mammalian cells)
Filtration
Protein A chromatogr.
Low pH hold viral inactivation
CIEX chromatogr.
AIEX flow through chromatogr.
Nano-filtration
UF/DF
Multiple cycles/continuous operation
Pre-treatment
Membrane crystalliser
Crystal recovery & washing
Crystal dissolution
Membrane-assisted crystallisation purification process

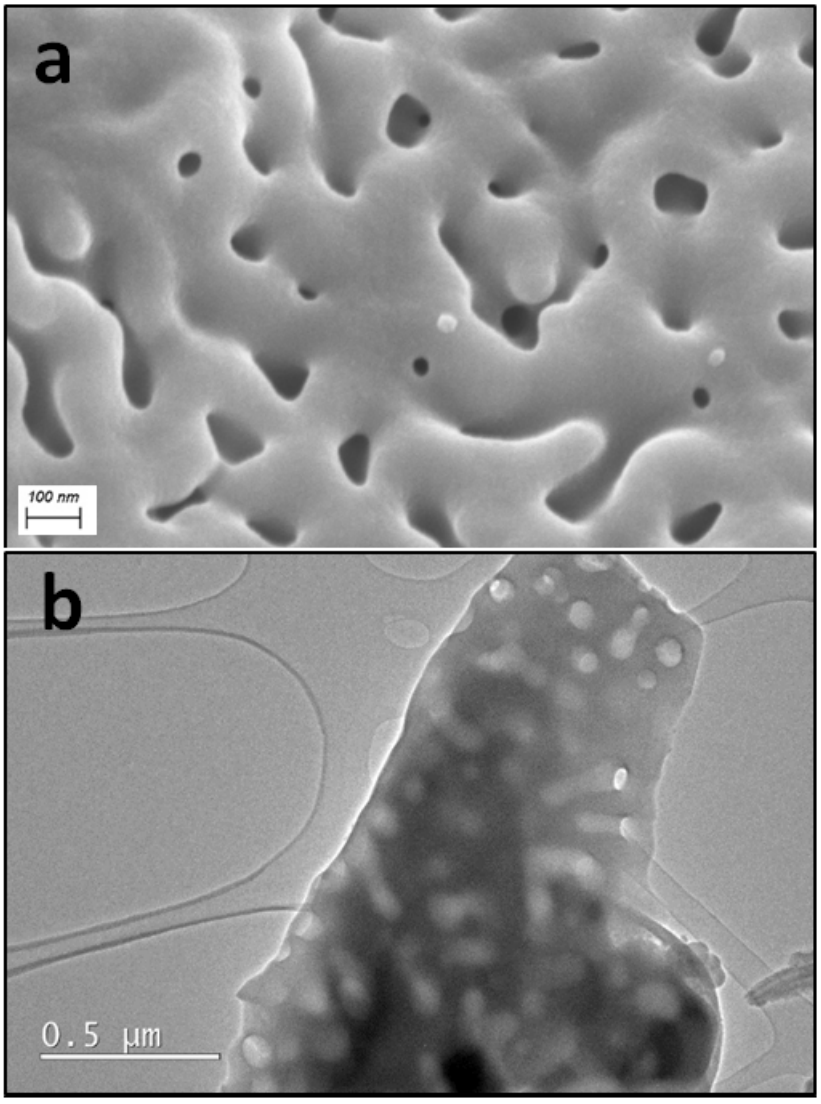

Stage 1
Prior Knowledge
Stage 2
Screening of Crystallization Conditions
D1
YES
Stage 3
Template Particle Preparation
D2
YES
Stage 4
Template-assisted Crystallisation
D3
YES
Stage 5
Membrane Design and Characterization
D4
YES
Stage 6
Particle integration to the Membrane
D5
YES
Stage 7
Membrane Crystallization: POC Validation
Stage 8
Product Characterization
D6
YES
Stage 9
Process Modelling and Design: scale up Prototyping
Goal
Robust template-assisted membrane crystallization process
NO
NO
NO
NO
D1: Is the crystallization process designed in a way so that the process conditions can be well optimised?
D2: Are the 3D-nano templates structure functionalized so that optimal particle size and pore size can be obtained?
D3: Is the selective crystallization behaviour robust enough?
D4: Is the membrane synthesis process robust enough?
D5: Is the membrane functionalized and ready to be used in the membrane crystallization stage?
D6: Is the concept of the membrane crystallization process proved in terms of obtaining the required yield and purity so that the whole process can be scaled up in the final stage?

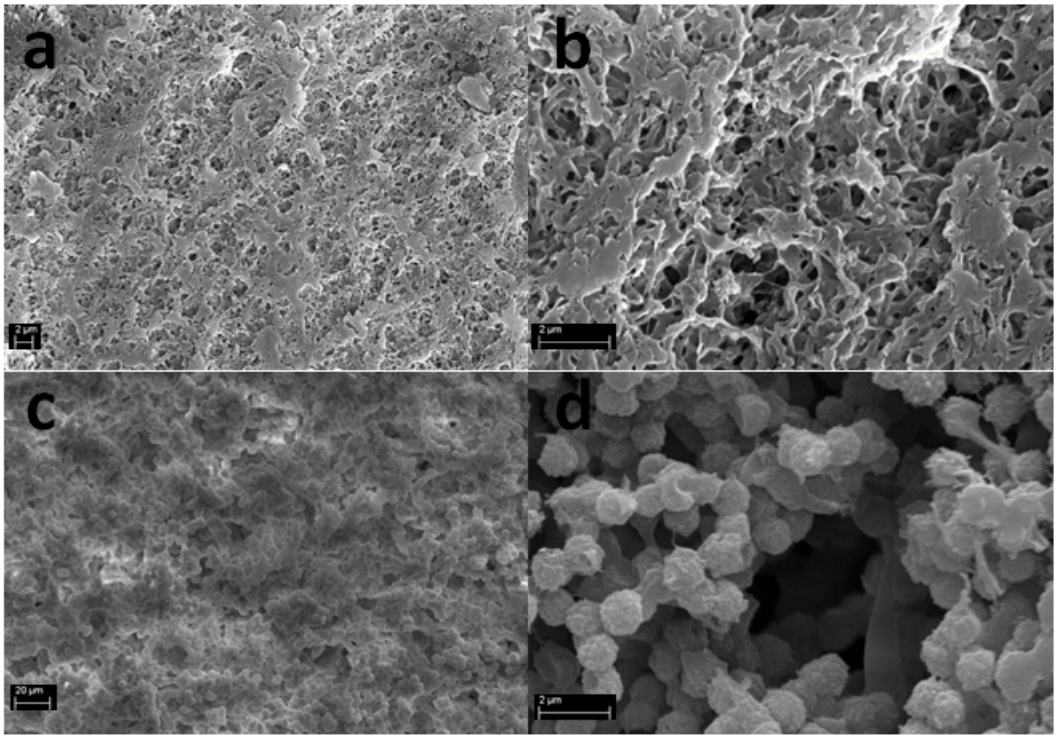

1E+05
1E+04
1E+03
1E+02
Nucleation rate (cm-3s-1)
1
1,1
1,2
1,3
1,4
1,5
Supersaturation (-)
LEVEL 1
LEVEL 2
LEVEL 3

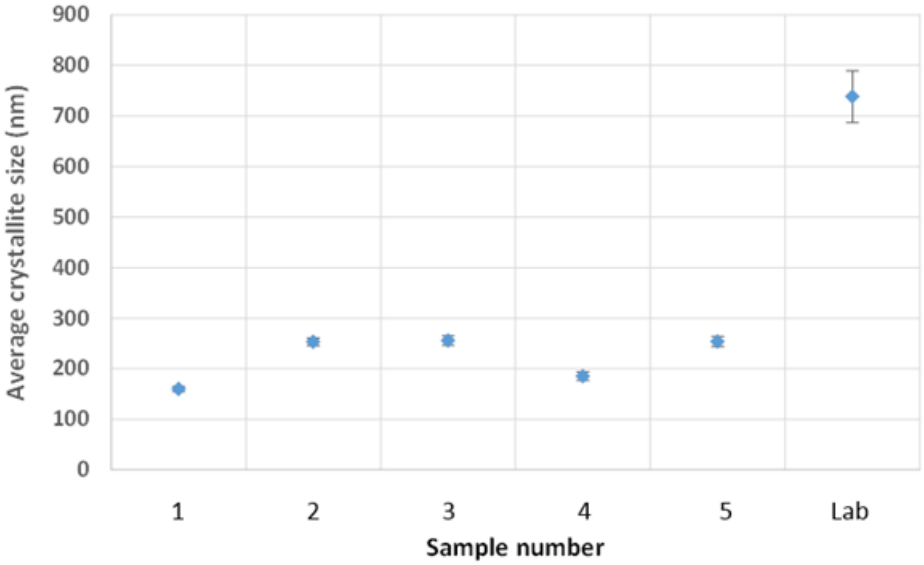

C_{PEG} (% v/v)
5
6
7
8
9
10
11
35
30
25
20
15
10
5
0
C_{mAbs} (mg/mL)
Precipitate
Crystals + Precipitate
Crystals
No Crystal
0.5
0.6
0.7
0.8
0.9
1
1.1
$C_{Na_2SO_4}$(M)

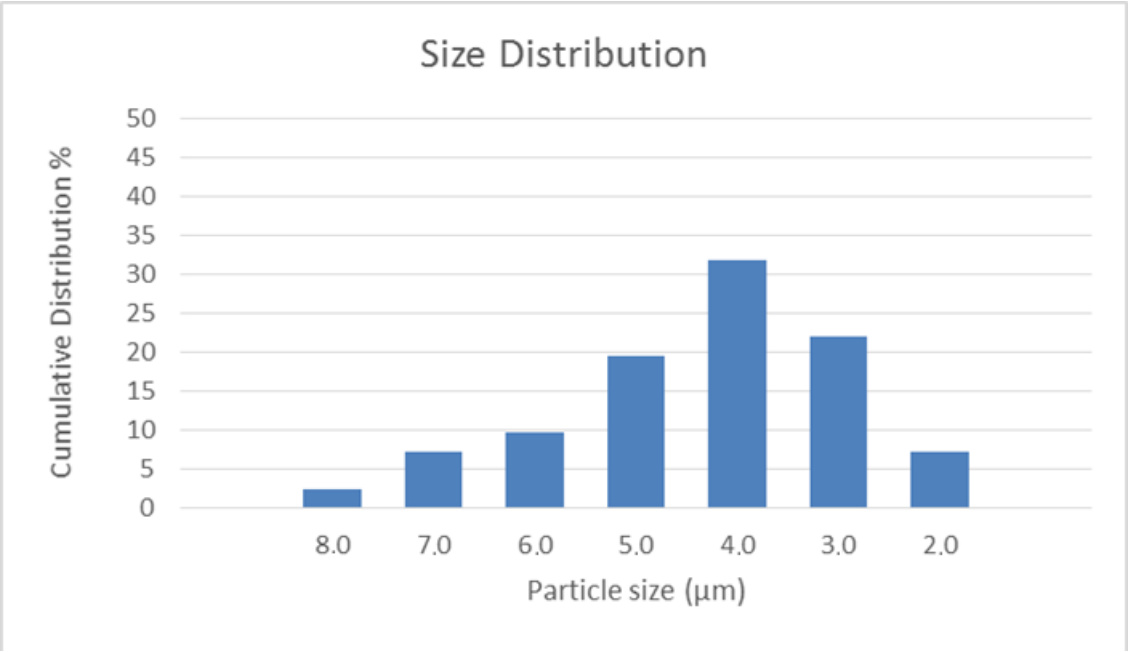

a)
b)
66Å
57Å
46Å
66Å

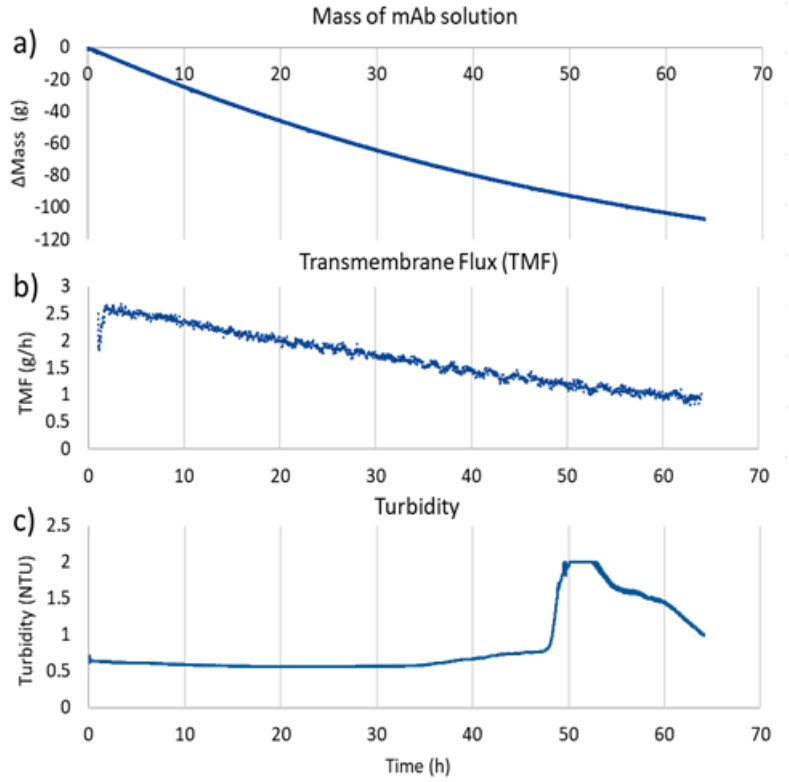

Intrusion for Cycle 1
0.0012
0.0010
0.0008
0.0006
0.0004
0.0002
0.0000
Differential Intrusion (mL/g/nm)
10,000
100
Pore size Diameter (nm)


a
100 nm
b
0.5 µm


a
2 µm
b
2 µm
c
20 µm
d
2 µm


900
800
700
600
500
400
300
200
100
0
Average crystallite size (nm)
1
2
3
4
5
Lab
Sample number


Size Distribution
Cumulative Distribution %
50
45
40
35
30
25
20
15
10
5
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
Particle size (µm)


a)
Mass of mAb solution
ΔMass (g)
0
-20
-40
-60
-80
-100
-120
0
10
20
30
40
50
60
70
b)
Transmembrane Flux (TMF)
TMF (g/h)
3
2.5
2
1.5
1
0.5
0
c)
Turbidity
Turbidity (NTU)
2.5
2
1.5
1
0.5
0
Time (h)