

Membranes for Molecular Separations

Ciclo de palestras em homenagem a Fernando Santana

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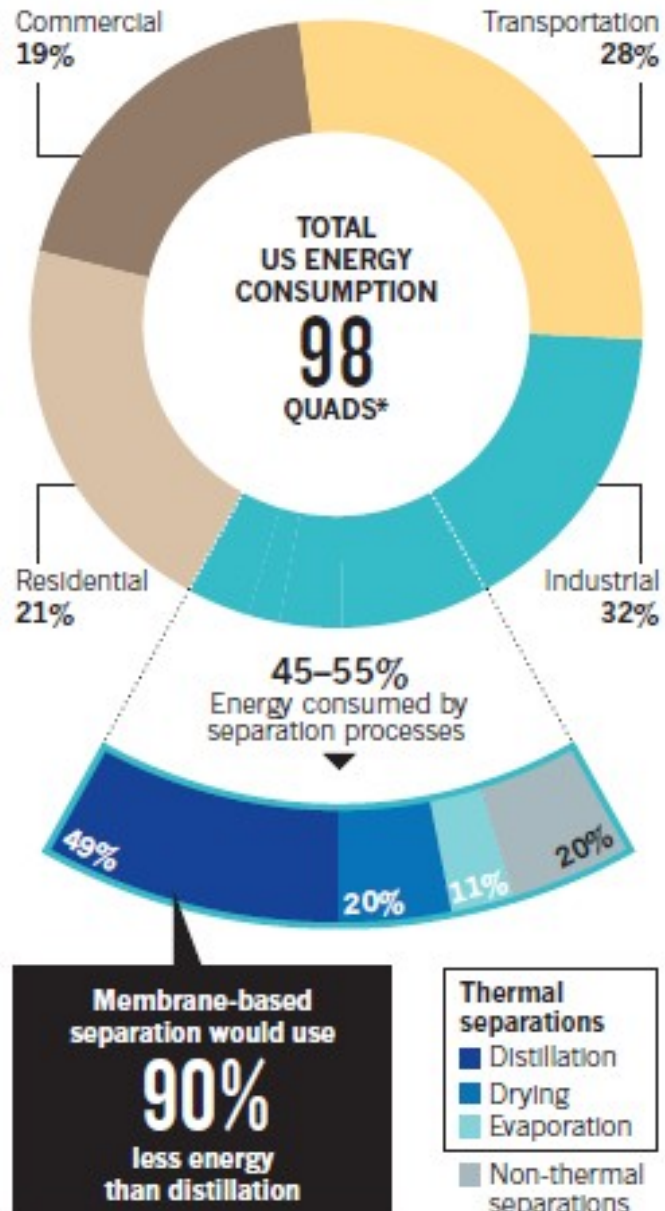
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- Molecular Separation and Organic Solvent Nanofiltration
- Membrane Fabrication
- From refining.....
-to polymers and exactymers

Molecular separations - a major energy consumer



Molecular separation processes account for between 40-70% of both the capital and operating costs in industry and 10-15% of the total US energy consumption

Vision 2020: 2000 Separations Roadmap

*Published by the Center for Waste Reduction Technologies
of the*

AIChE
In cooperation with

Scholl and Lively, Nature (2016)

532 pp435-437

Organic Solvent Nanofiltration (OSN) - the future for molecular separations in organic systems?

- Water processing - Desalination - Reverse Osmosis (RO) dominates the market over multiple effect evaporation (high energy).
- Can membranes produce the same paradigm change for organic liquids processing?



World Scale RO Plants

100,000 - 300,000 m³ d⁻¹

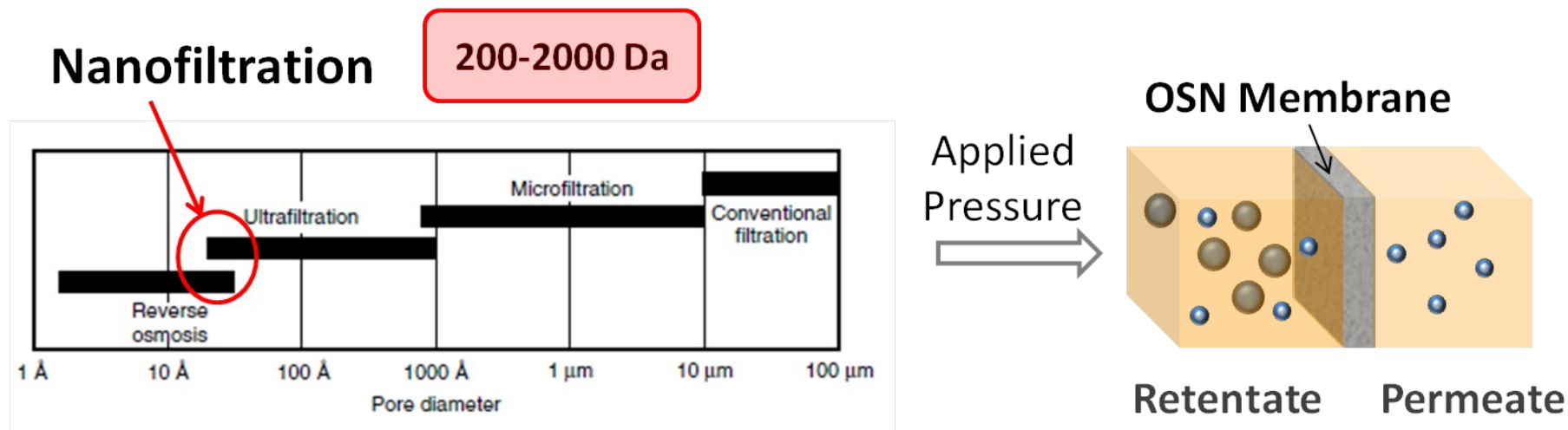


World Scale Oil Refineries

50,000 - 100,000 m³ d⁻¹

Organic Solvent Nanofiltration (OSN) - the future for molecular separations in organic systems?

OSN → Emerging membrane technology for separation and purification processes involving organic solvents.



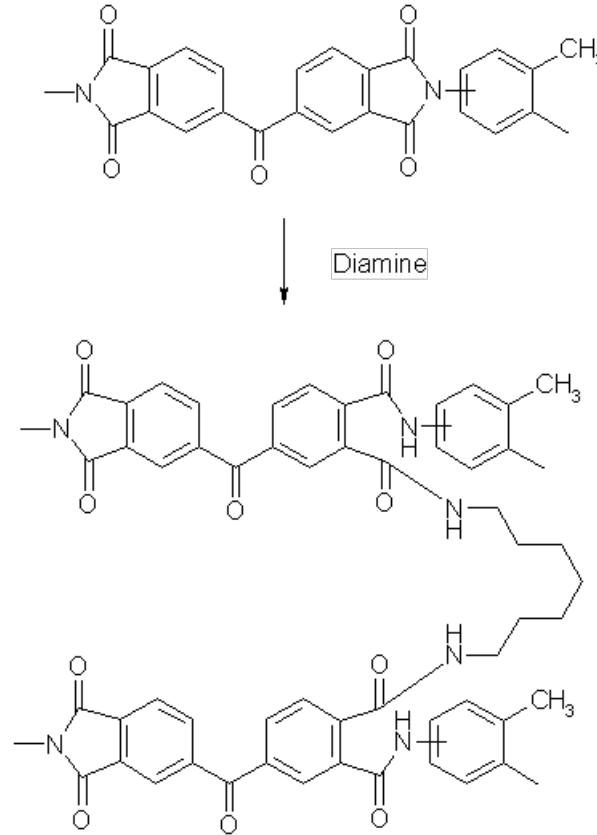
OSN membranes must preserve their separation characteristics in contact with **organic solvents**.

Fabricating molecular separation membranes - phase inversion

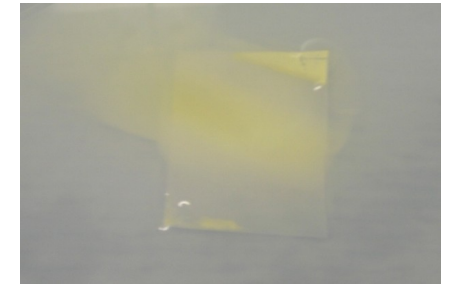


OSN membrane fabrication: solvent stability

Post-formation **cross-linking** of polyimide membranes via diamines using **established chemistry**

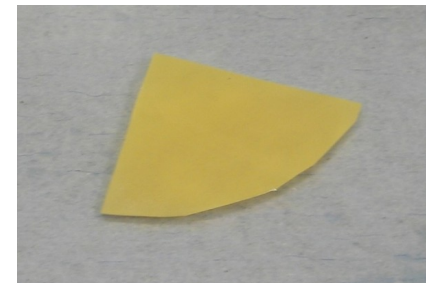


BEFORE



1 MINUTE

AFTER IMMERSION IN DMF



2 YEARS!!!

(12) **United States Patent**
Livingston et al.

(10) **Patent No.:** US 8,894,859 B2
(45) **Date of Patent:** Nov. 25, 2014

US See-Toh et al., *J. Membr. Sci.* **301** (2007), pp1-10

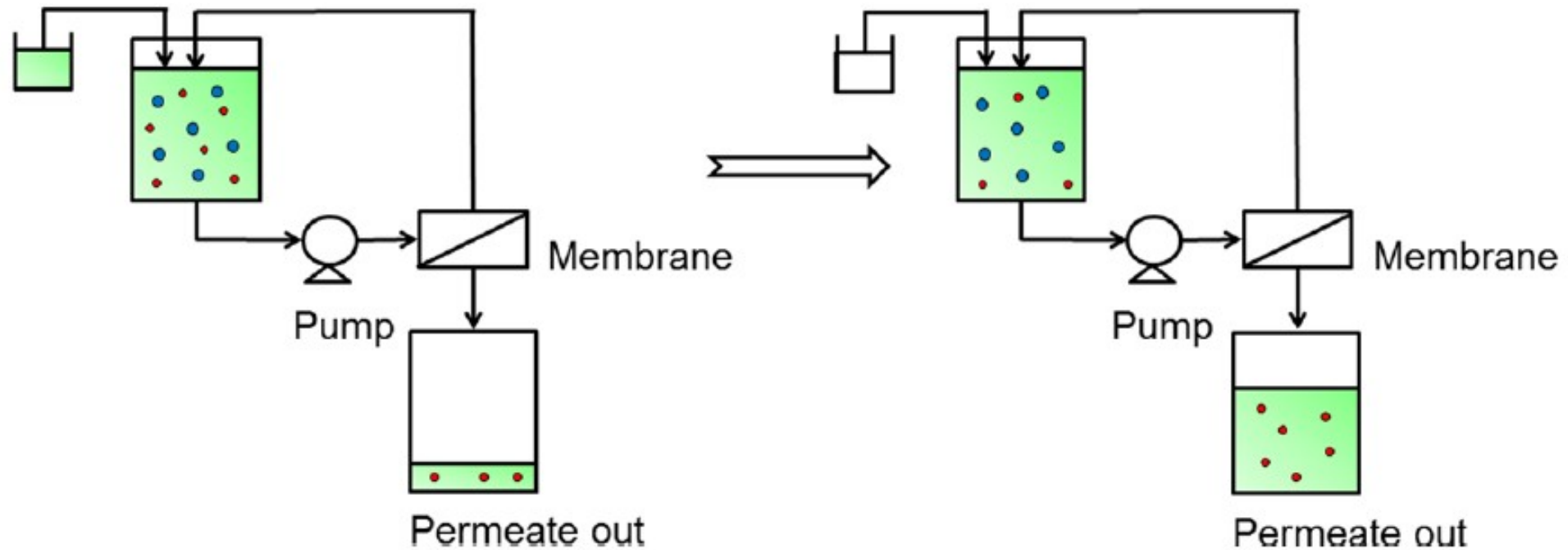
(54) ASYMMETRIC MEMBRANES FOR USE IN NANOFILTRATION

USPC 210/652; 210/490; 210/500.39; 264/41; 264/48

OSN for purification

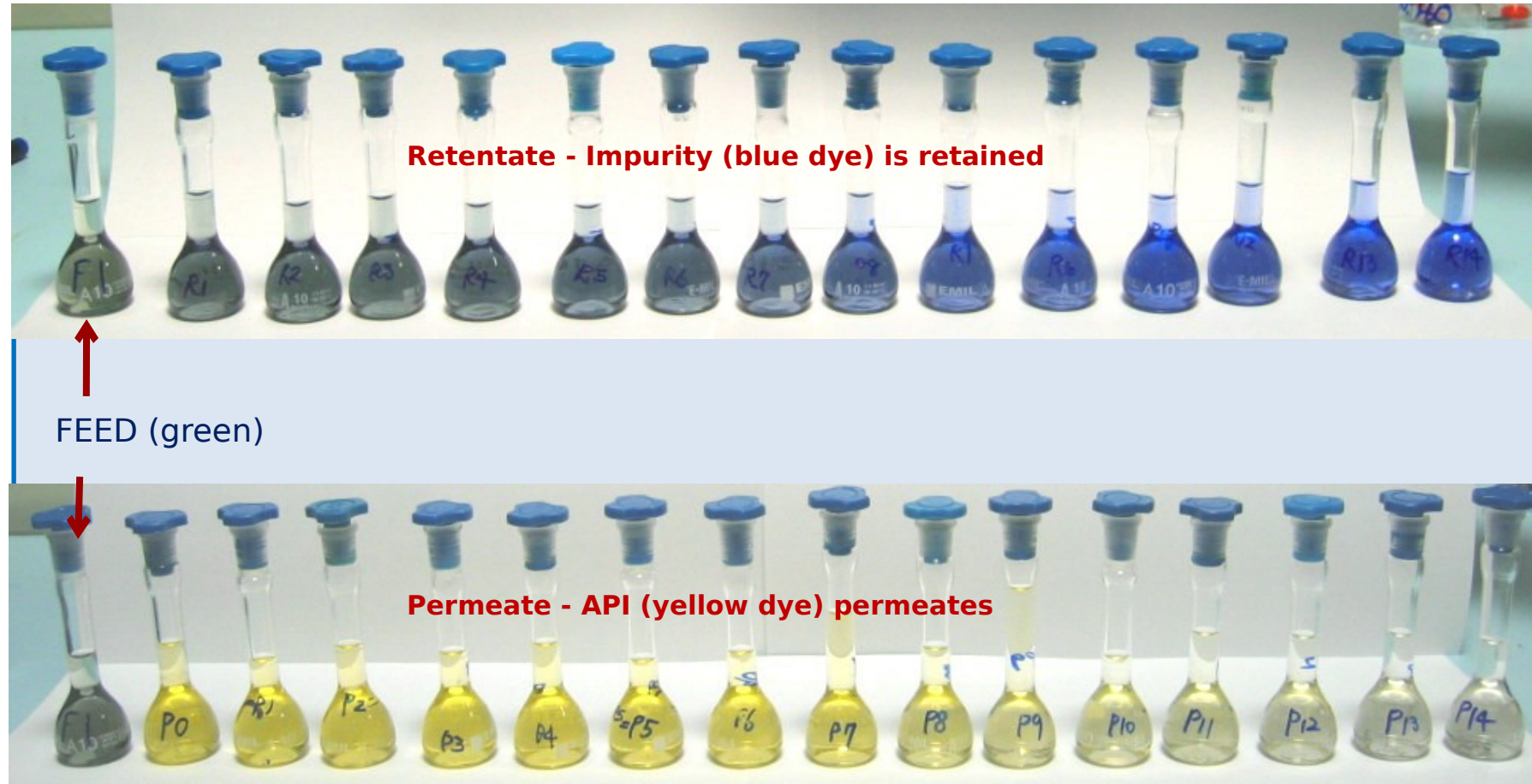
(c) Purification

Defining feature: at least two solutes and one solvent



OSN for purification

Constant Volume Diafiltration □ separate model API (yellow dye, MW=274) from model large Impurity (blue dye, MW=826) in methanol.



OSN for purification

- Separation of coloured impurity from API at Astra Zeneca by OSN *

(3a) Starting material containing high MW coloured compound

(3b) Coloured impurity difficult to remove via extraction

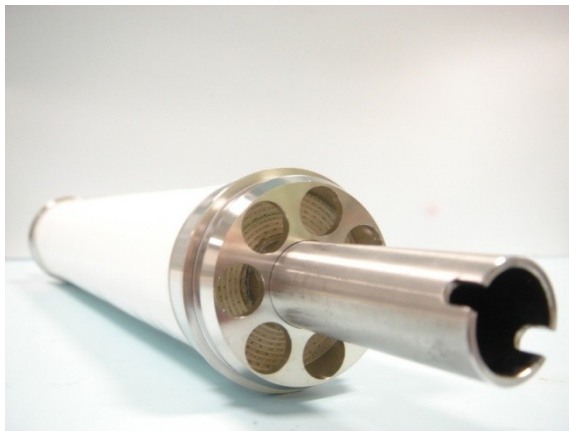
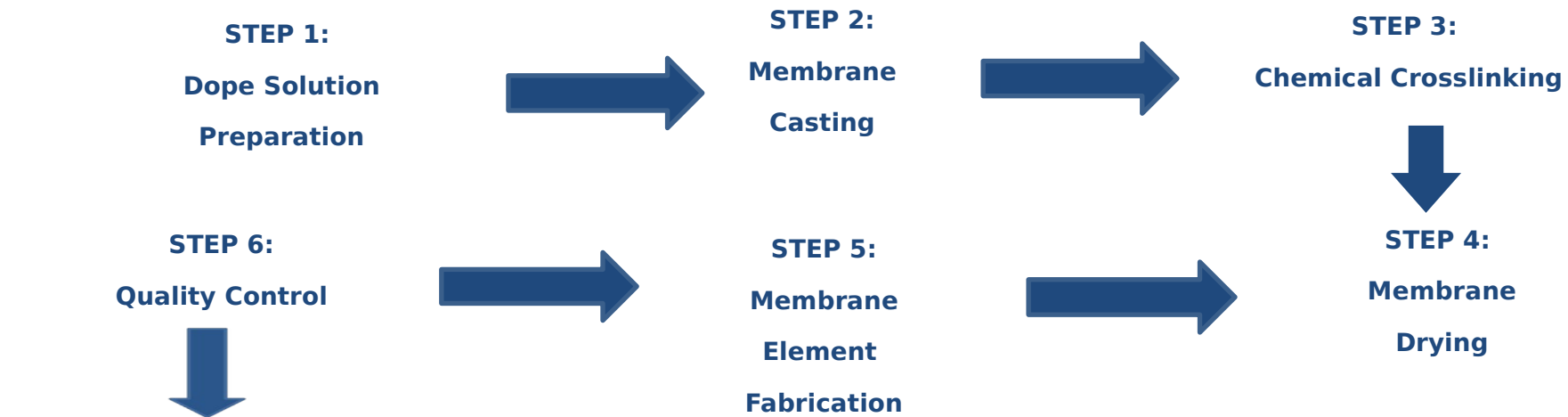
(3c) Product after OSN purification.
Nice white powder!

Nanofilter solution so that API passes through membrane with solvent and impurity is retained



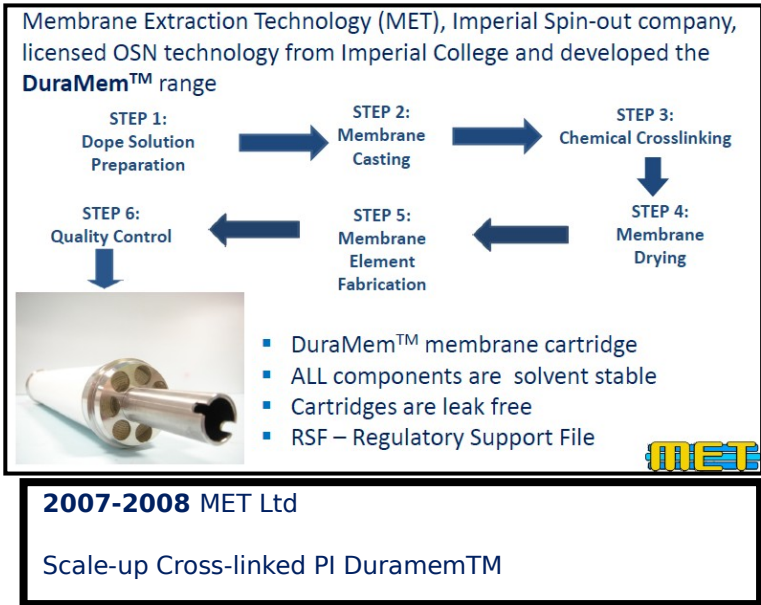
DuraMem™ FABRICATION PROCESS

Founded Membrane Extraction Technology (MET) licensed OSN technology from Imperial College and developed the **DuraMem™** range



- DuraMem™ membrane cartridge
- ALL components are solvent stable
- Cartridges are leak free
- RSF - Regulatory Support File

Commercialisation of crosslinked PI OSN membranes



Evonik MET Ltd

2010 Evonik Acquisition of MET Ltd

- MET acquired by Evonik AG 1 March 2010
- Evonik have invested in new facilities and space for production of membranes and membrane modules
- Operational since June 2012
- Fabrication of a range of membranes and modules up to 8" x 40" spiral modules

2006-2007
Invention of Crosslinked Polyimide Membranes
US Patent 8,894,859

AFTER IMMERSION IN DMF



2008 onwards
Duramem™ Commercial Installations



Membranes for Molecular Separation

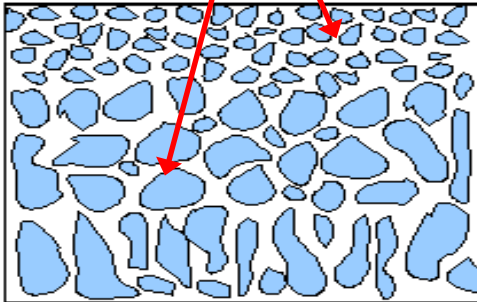
Adventures in Nanoland

Organic Solvent Nanofiltration (OSN)

**Integrally skinned asymmetric (ISA)
membrane**

ONE step process

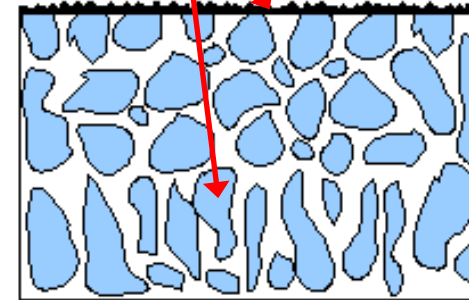
same material



**Thin Film composite (TFC)
membrane**

MULTIPLE step process

different material



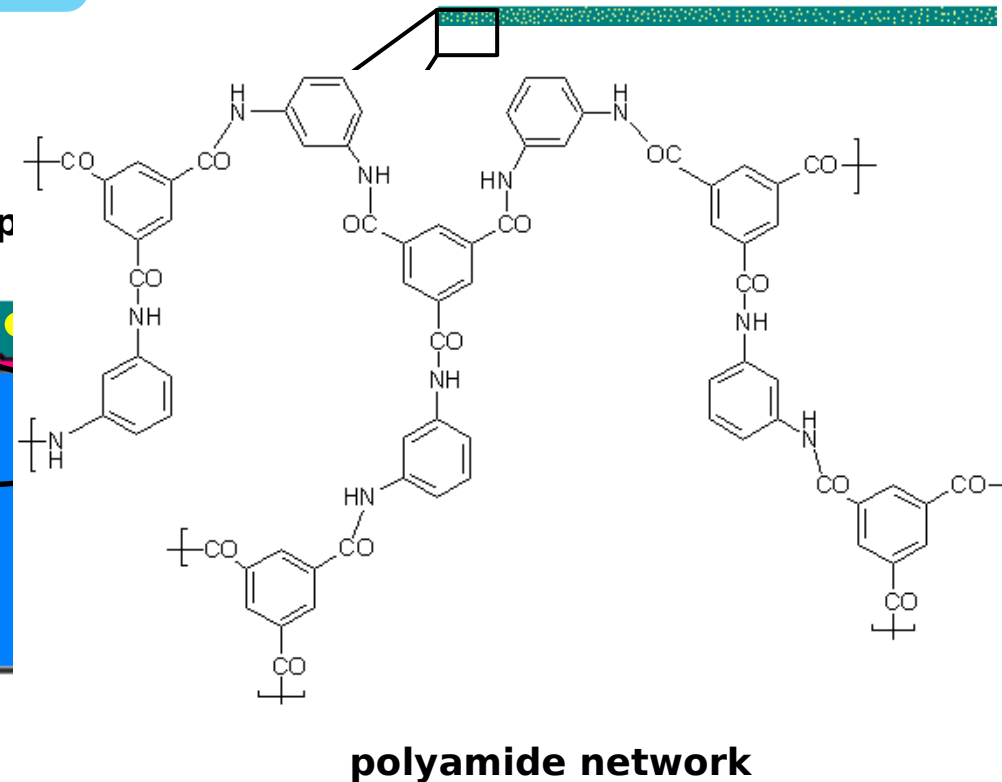
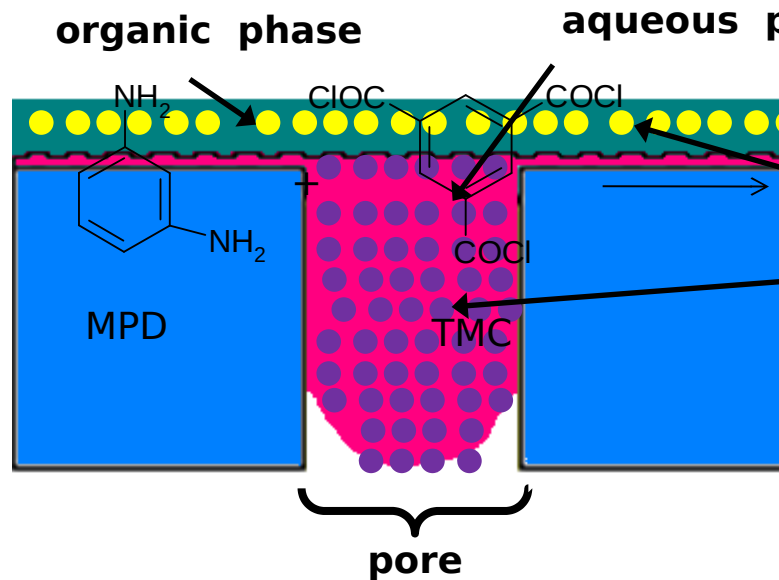
Membrane Fabrication - the search for permeance

Thin Film Composites By Interfacial Polymerisation

aqueous amine solution

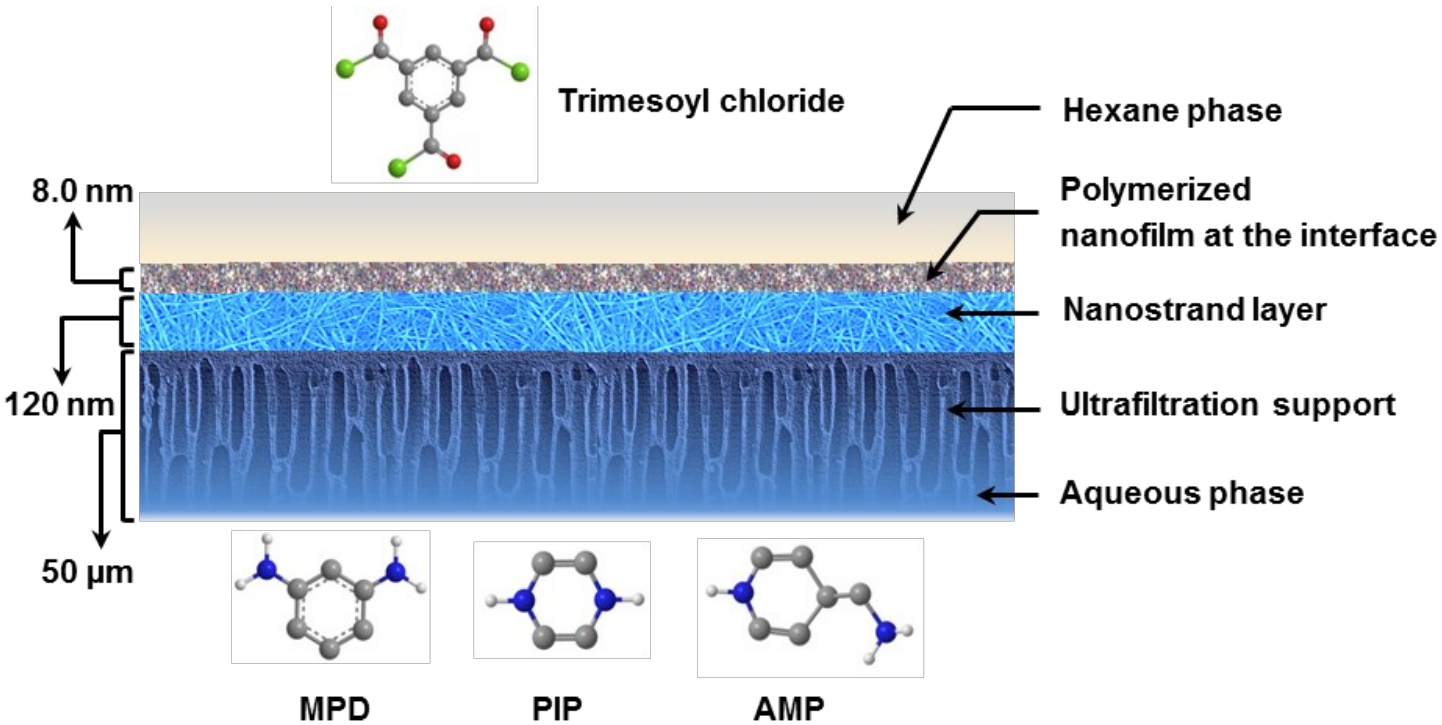
organic acid chloride solution

- *m* - phenylenediamine (MPD)
- trimesoyl chloride (TMC) in hexane

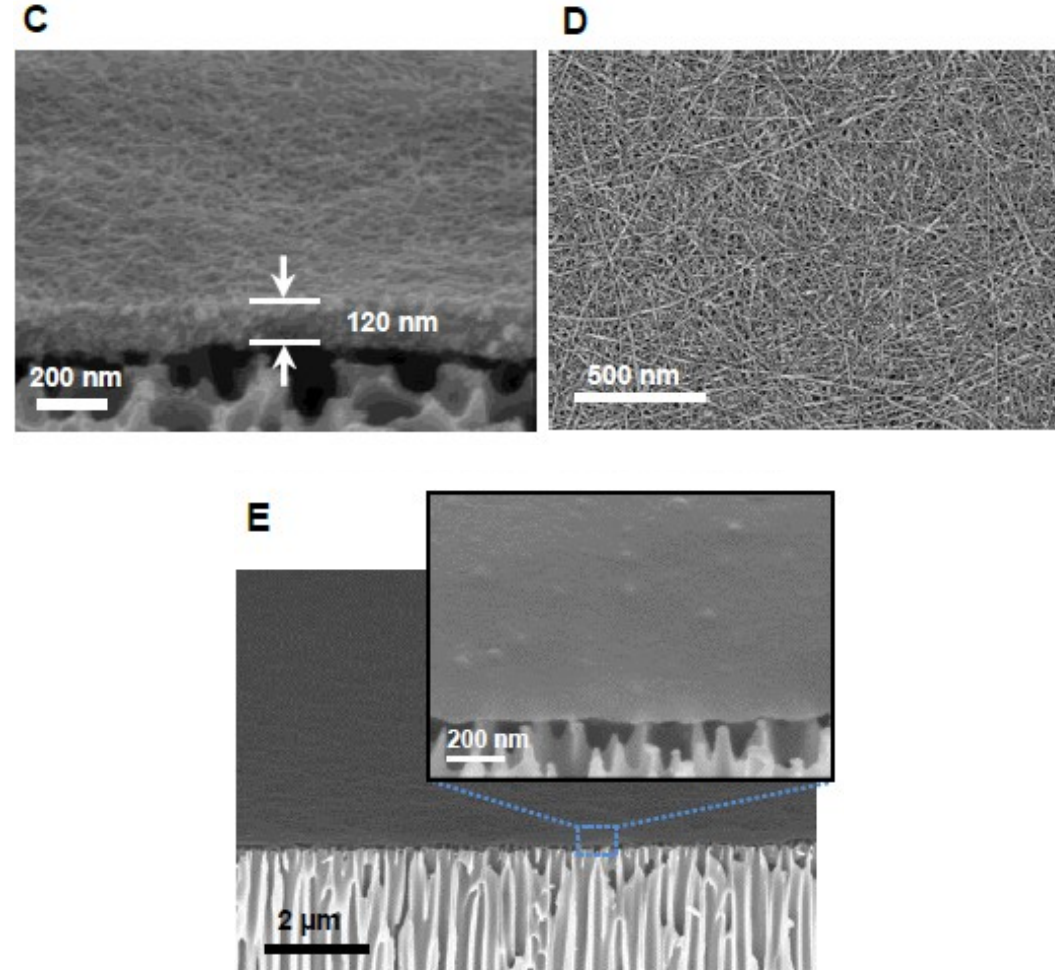


Nanoland - sub 10nm polyamide films

✓ Fabrication of highly cross-linked ultrathin nanofilms

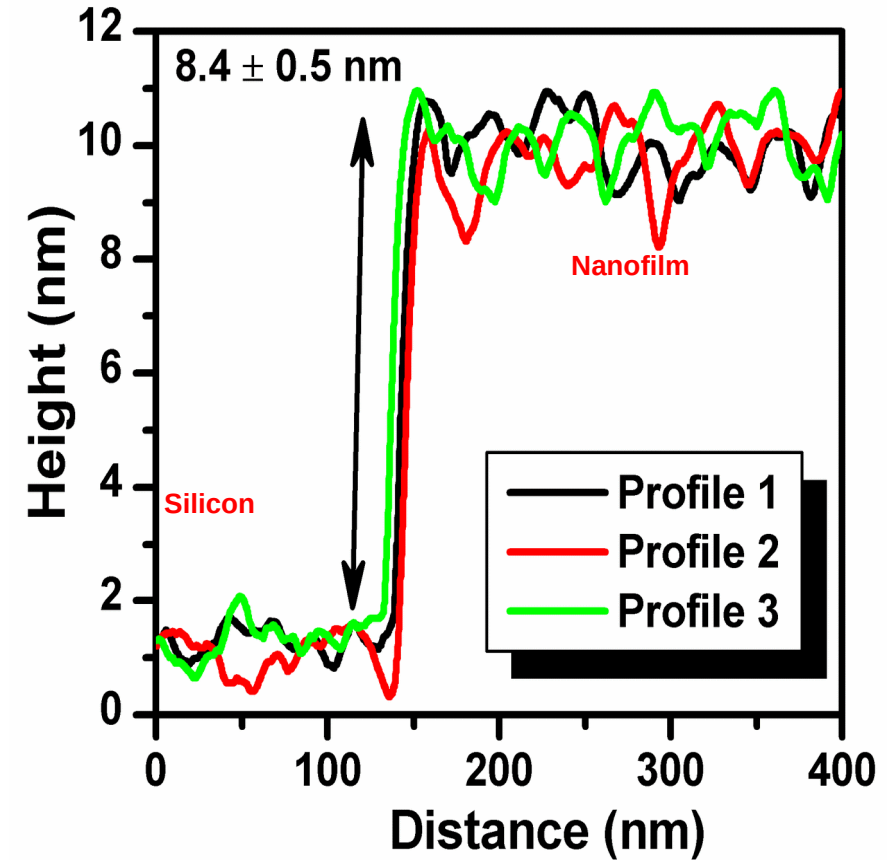
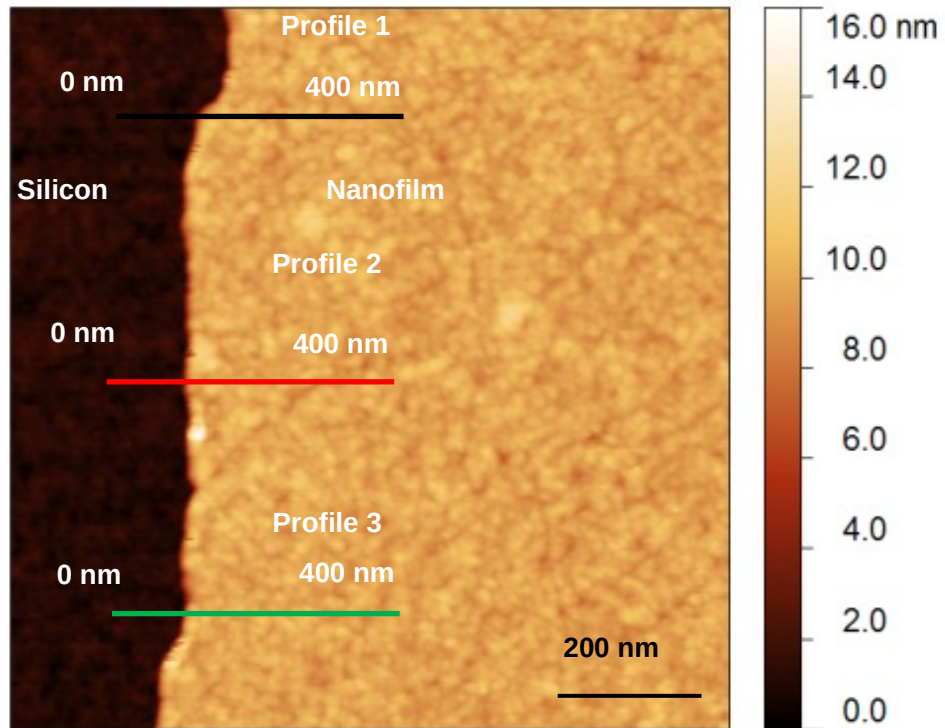


MPD: m-Phenylenediamine; PIP: Piperazine; AMP: 4-(Aminomethyl)piperidine



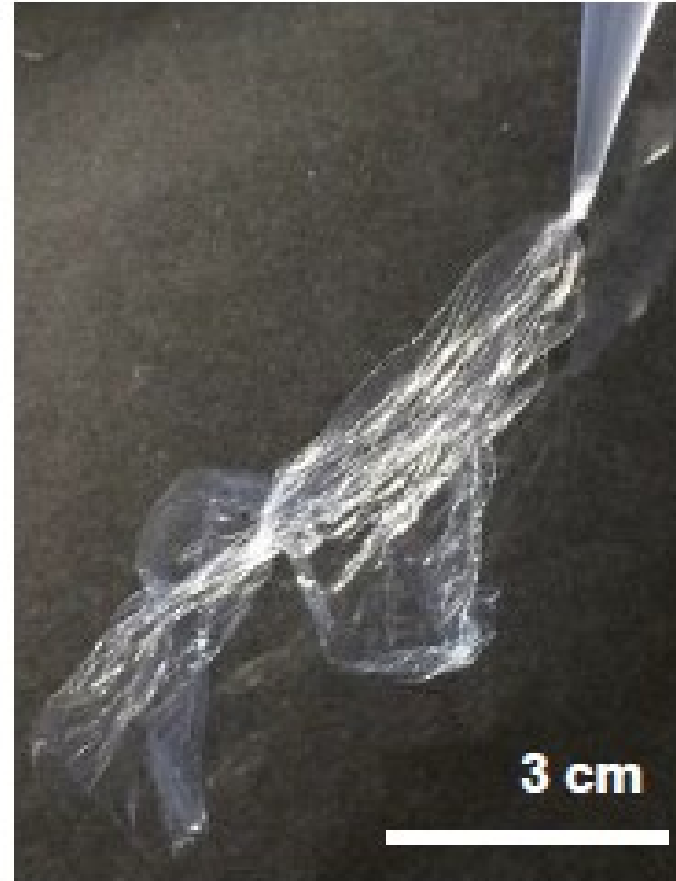
Nanoland - Sub 10nm polyamide films

✓ Properties of highly cross-linked ultrathin nanofilms



Nanoland - Sub 10nm polyamide films

- ✓ Properties of highly cross-linked ultrathin nanofilms

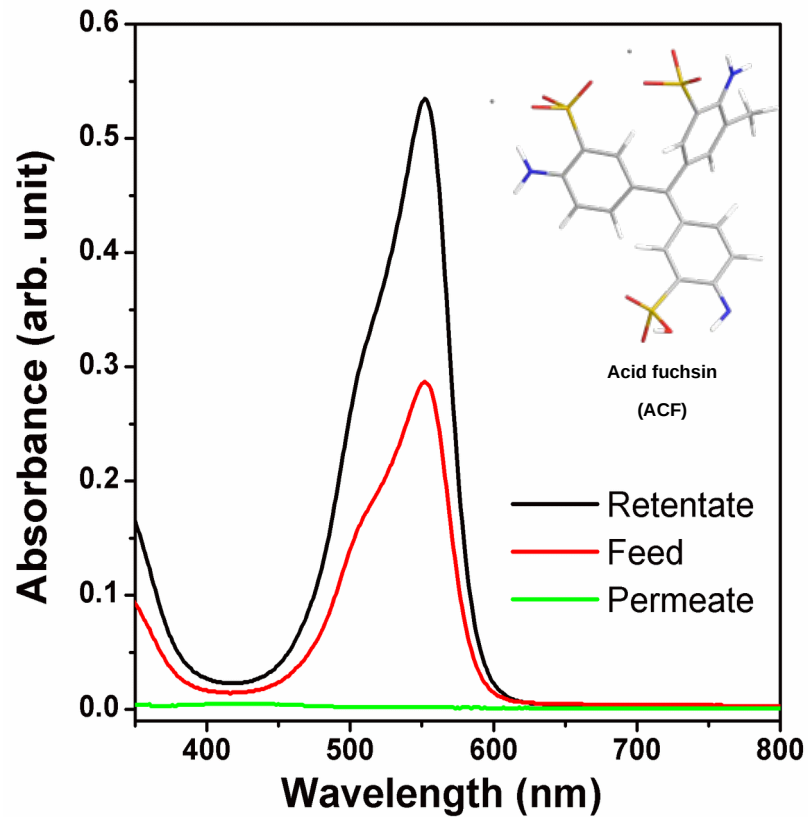


Nanoland- Sub 10nm polyamide films

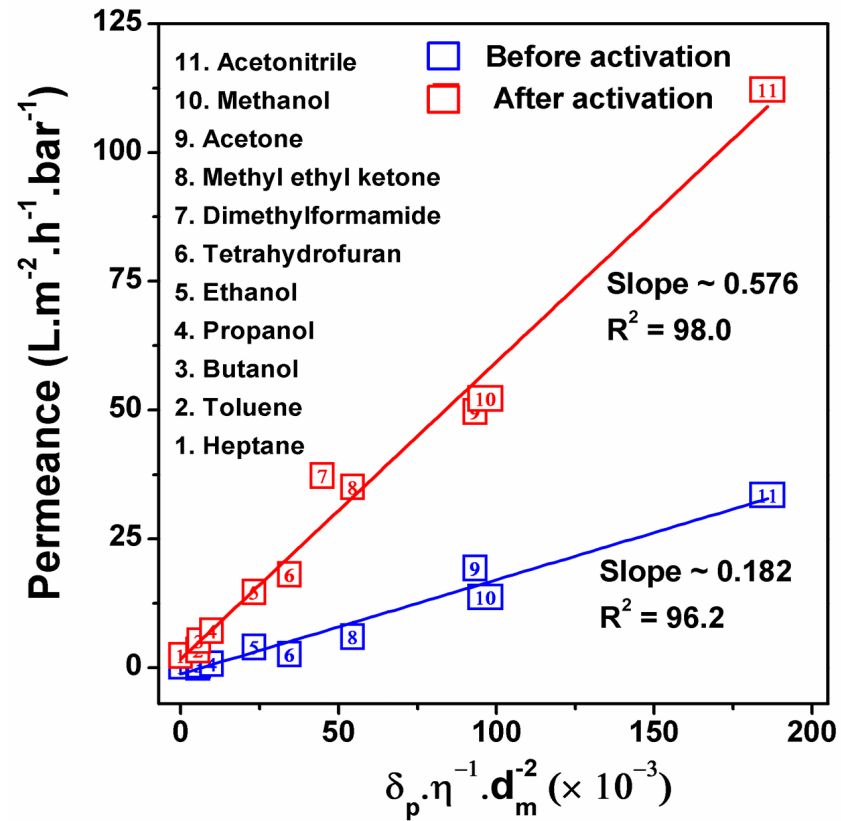
✓ Performance of highly cross-linked ultrathin nanofilms

Rejection of dye

(ACF - 585 g mol⁻¹)



Solvent permeance



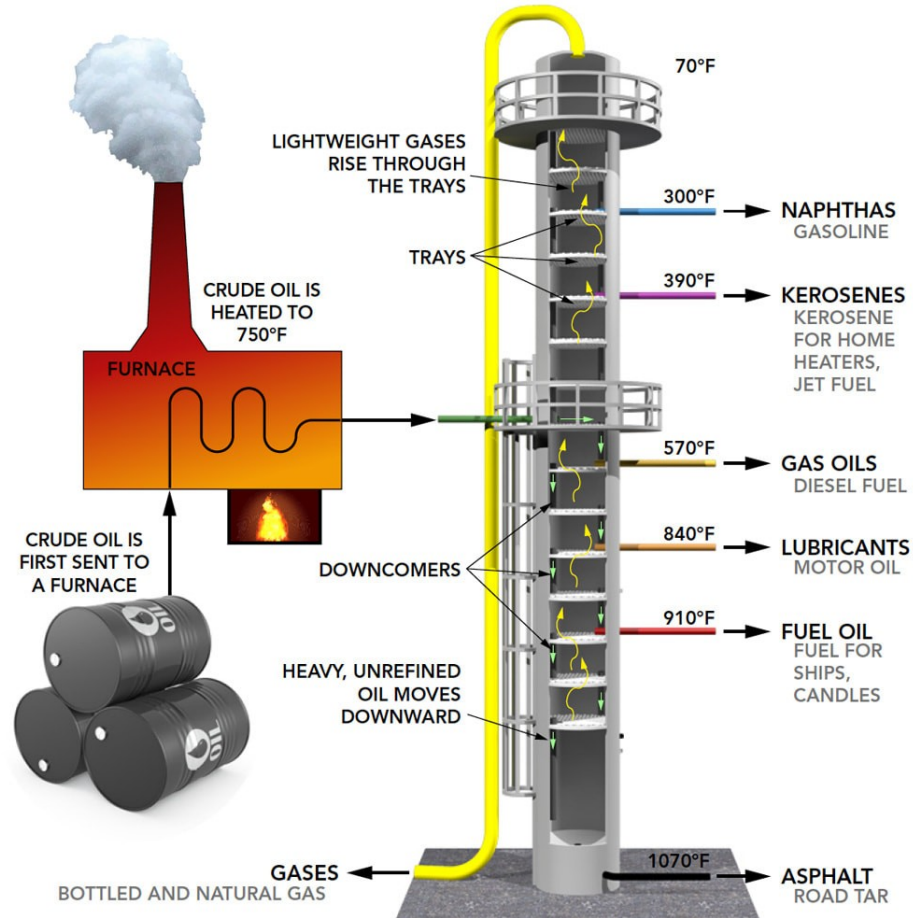
Membranes for Molecular Separations

Refining

Separation of complex mixtures

Separation of complex organic mixtures

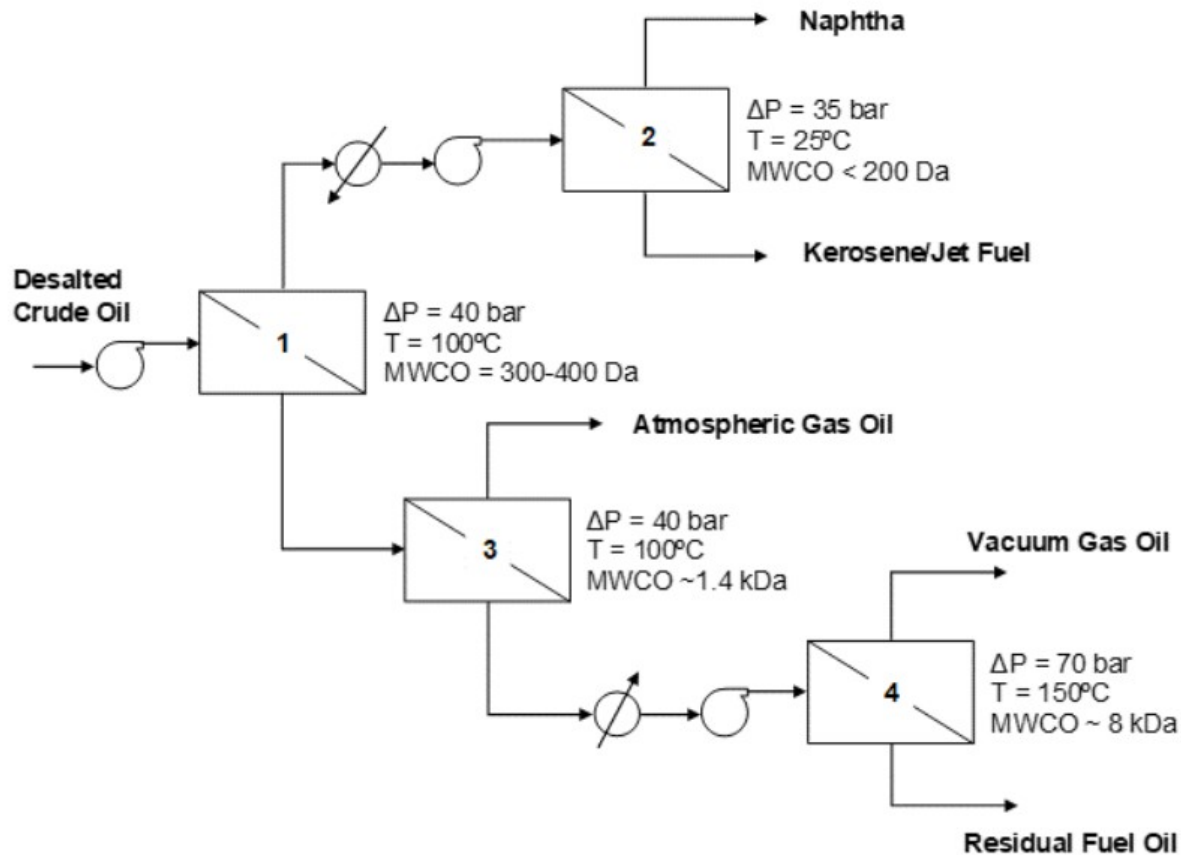
✓ Crude Oil Refining



- ✓ Conventional crude refining separates molecules based on boiling points through repeated evaporation and condensation cycles (phase change)
- ✓ It results in significant energy consumption, and carbon area foot-print
- ✓ It would be advantageous to fractionate whole crude and/or its various components into conventional distillate fractions without the requirement for a thermal phase change (boiling)

Separation of complex organic mixtures

✓ Crude Oil Refining

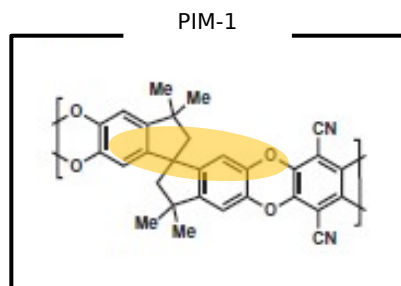


✓ Using different membranes at each stage, the crude can be fractionated based on size and class without boiling (phase change)

✓ The key is to **develop rigid membranes which are available to separate light hydrocarbon stream without swelling**

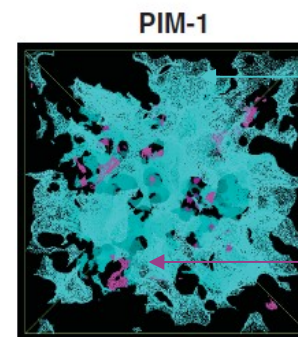
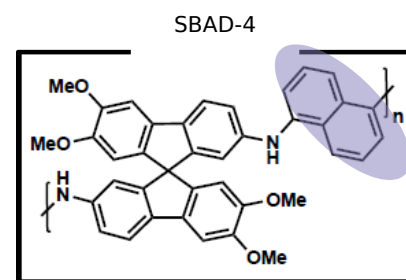
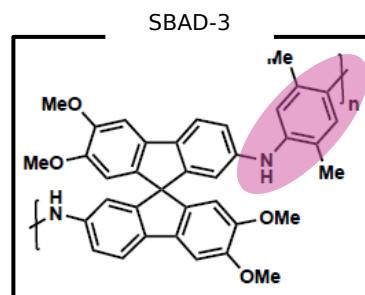
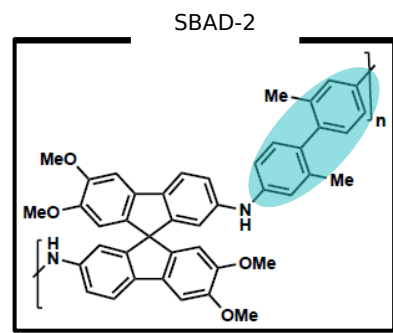
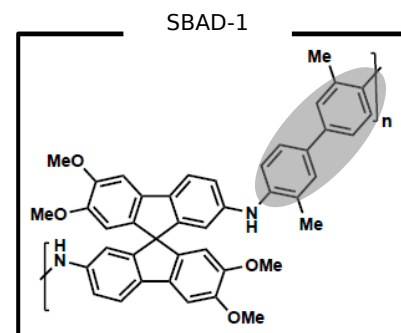
Separation of complex organic mixtures

✓ Crude Oil Refining



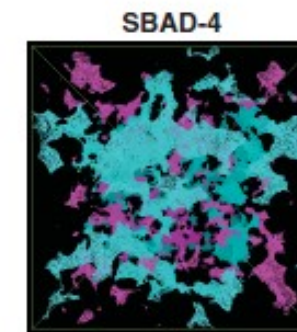
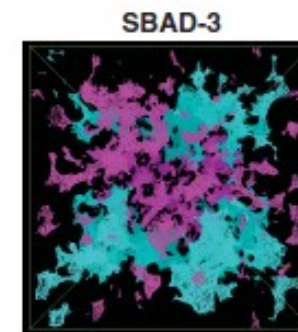
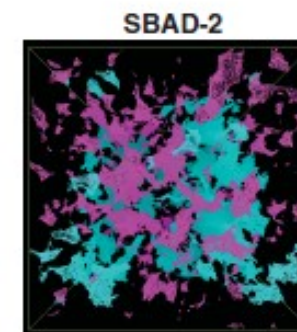
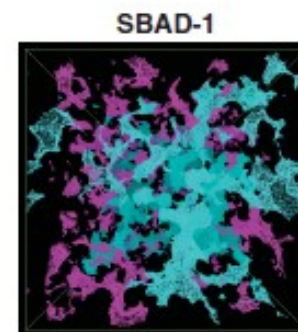
Introducing rigid moieties makes rigid structure
and microporosity

SBAD =
Spiro-Bifluorene Aryl Daimine



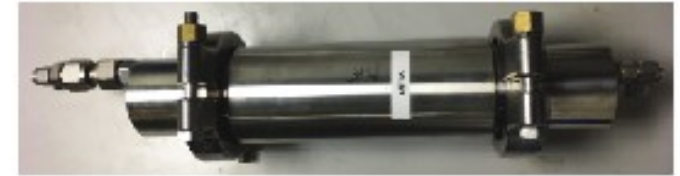
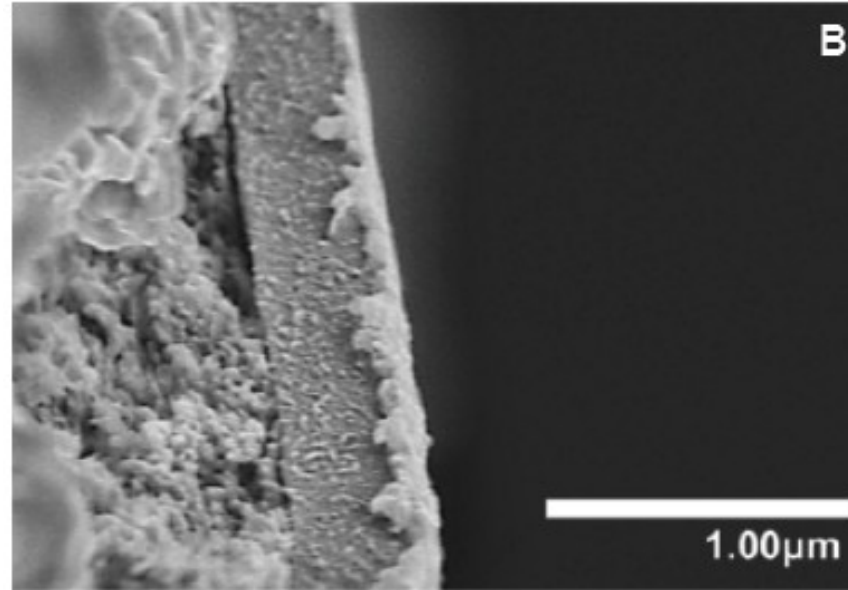
Interconnected pore
structure

Non-accessible pore
(rigidity)



Separation of complex organic mixtures

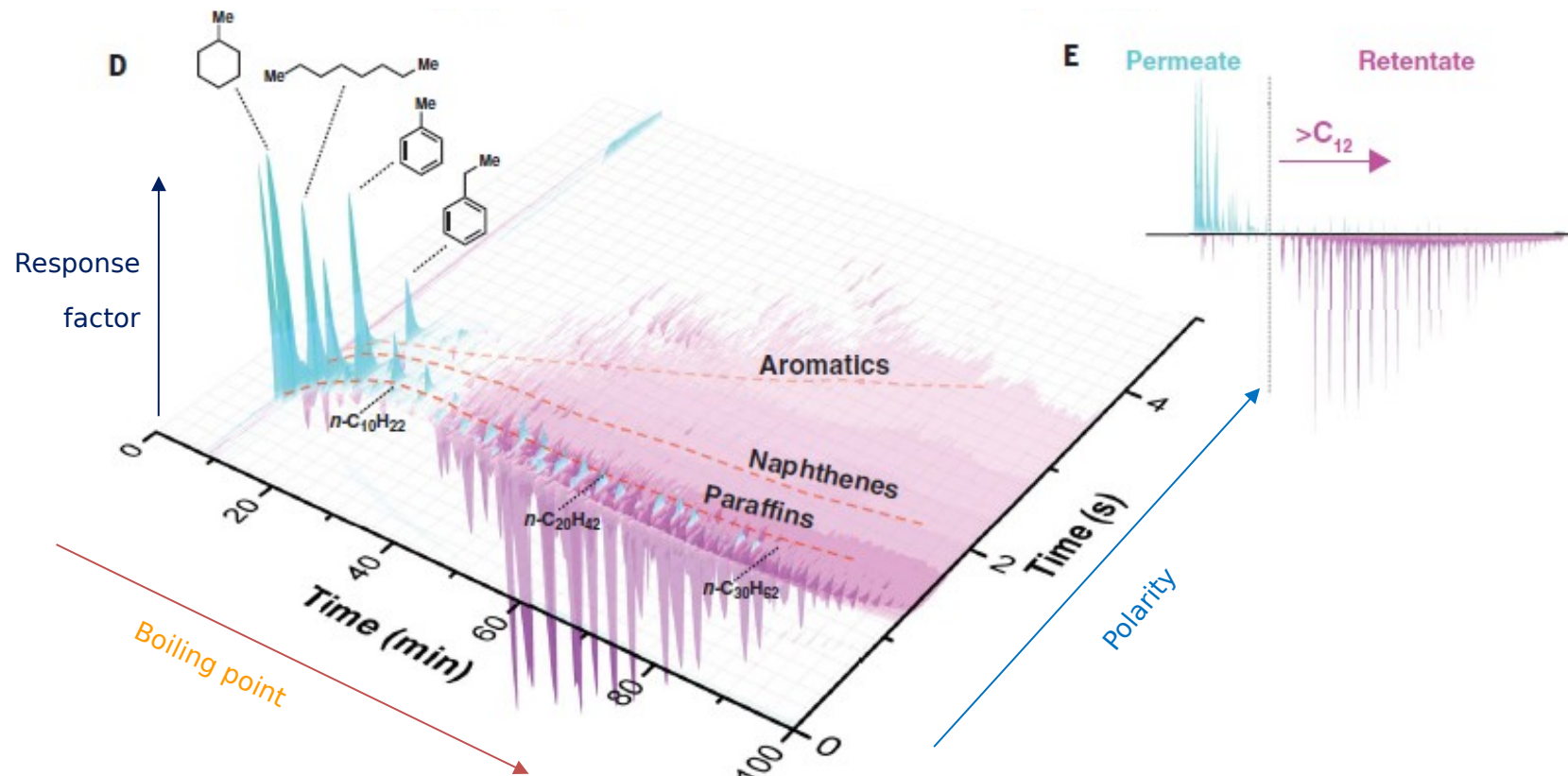
✓ Crude Oil Refining



- ✓ SBAD dissolved in chloroform and cast onto crosslinked polyetherimide support membranes
- ✓ Film thickness a few hundred nm
- ✓ Membrane modules were fabricated to demonstrate scale-up potential

Separation of complex organic mixtures

✓ Crude Oil Refining

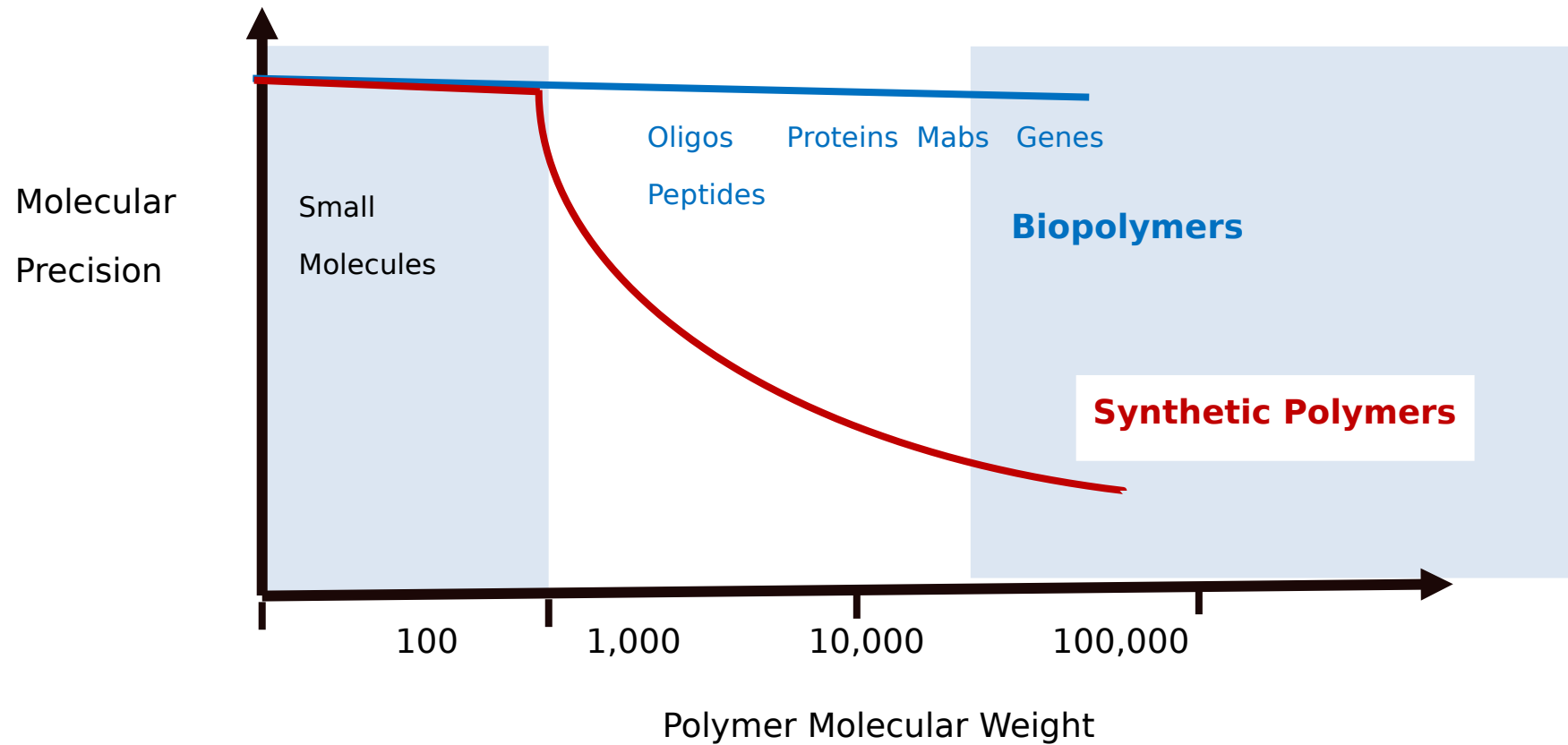


✓ The actual crude oil can be separated using SBAD-1 and analysed with GCxGC-FID (Exxon)

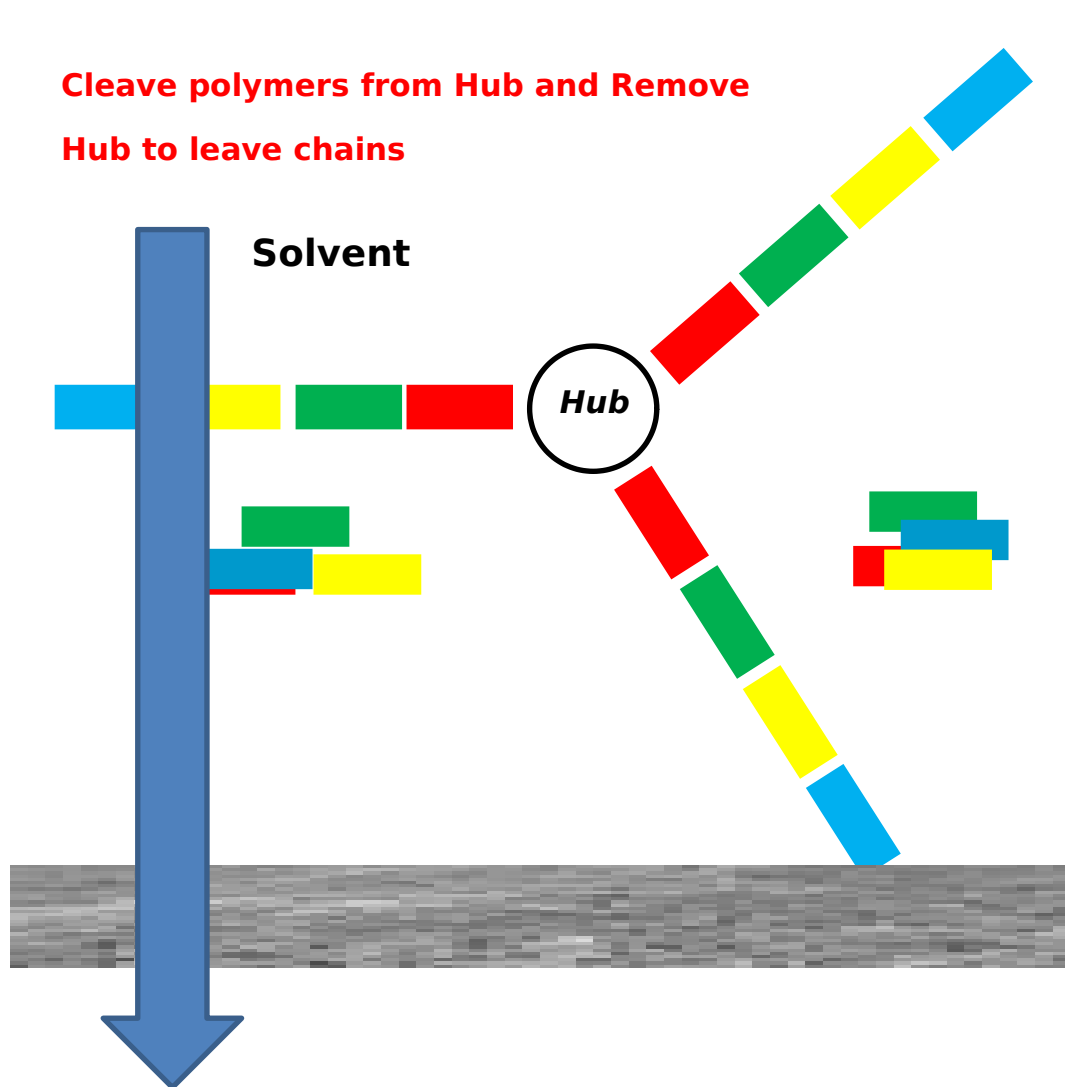
Membranes for Molecular Separations

Polymers and Exactymers

Exact Polymer Synthesis → Defined Monomer Sequences



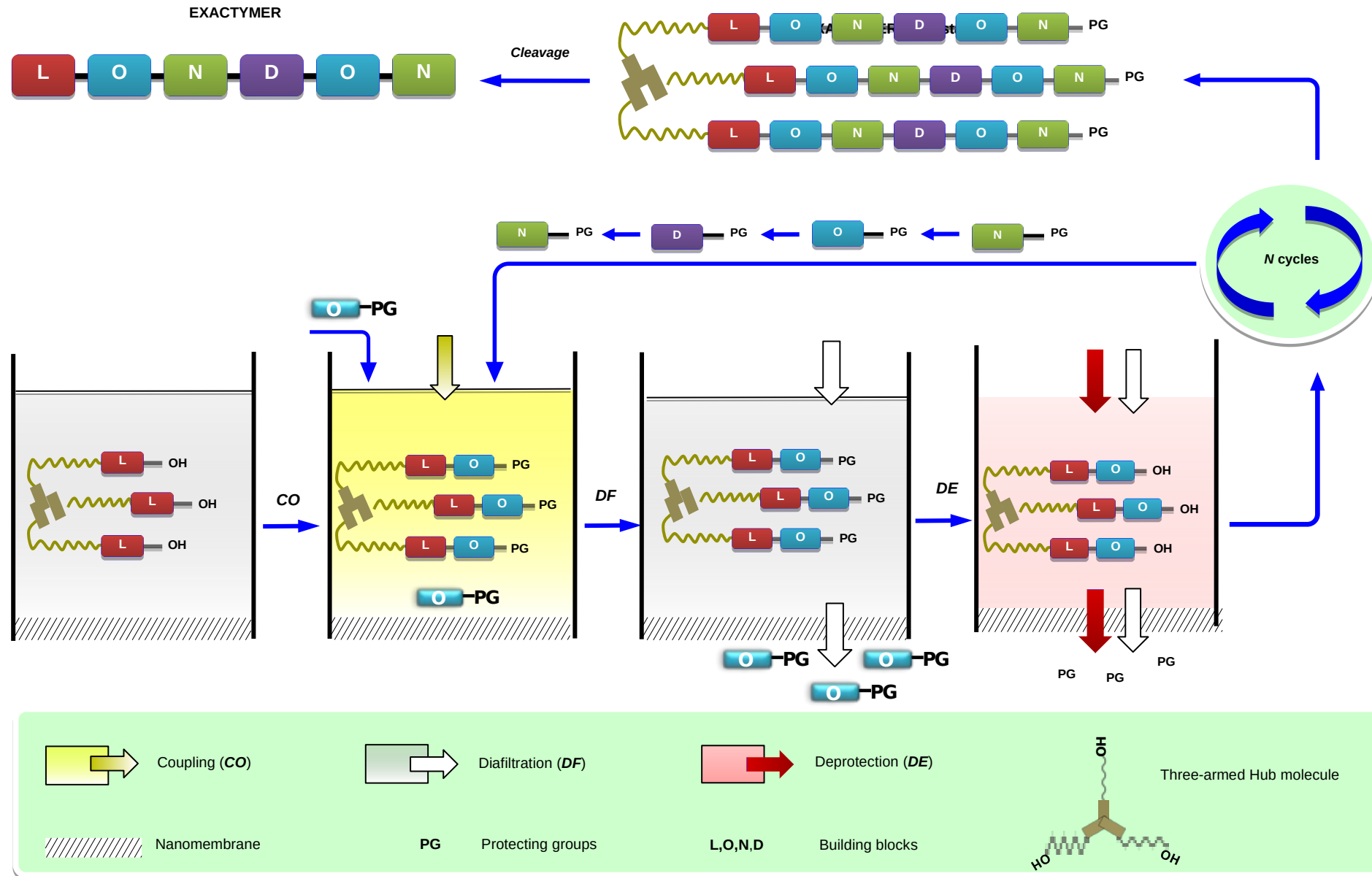
Iterative Synthesis Using Nanostar Sieving

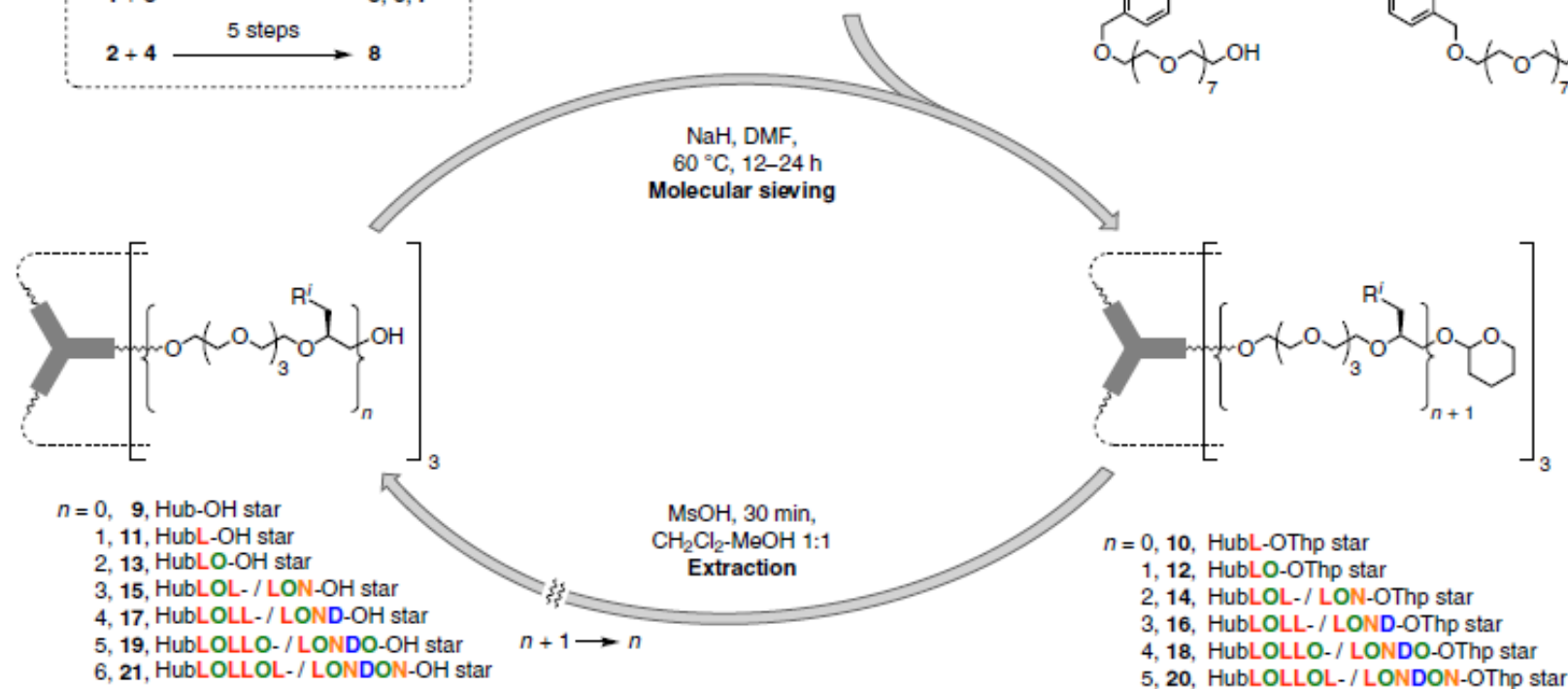
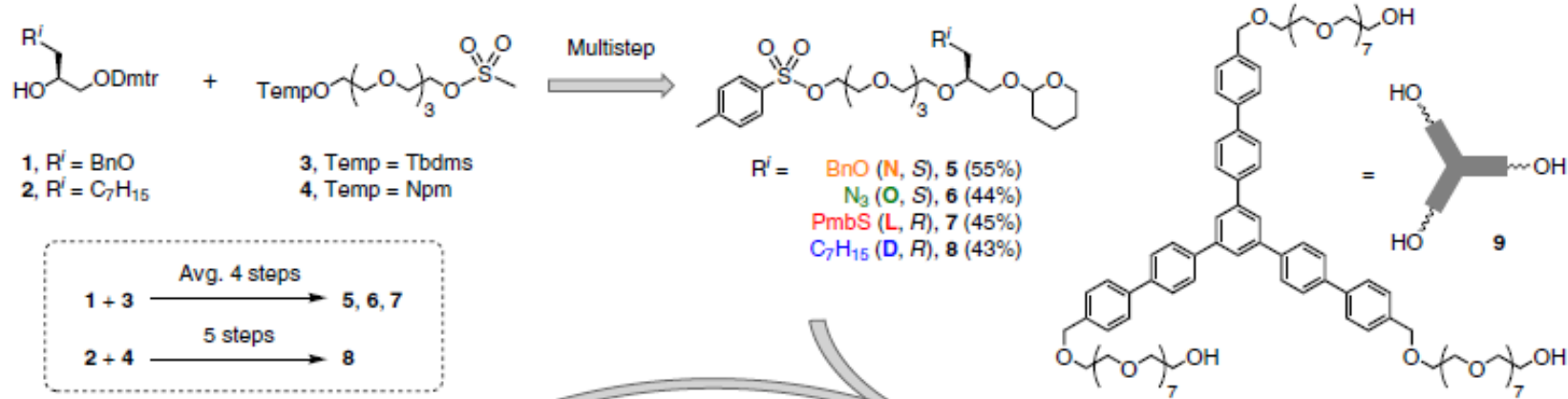


Applications

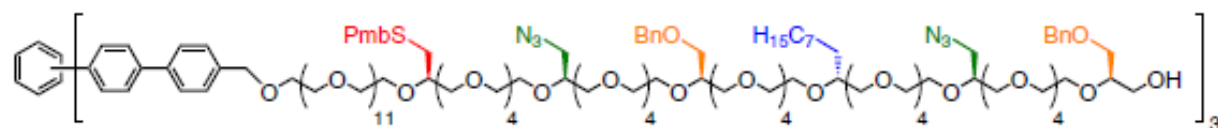
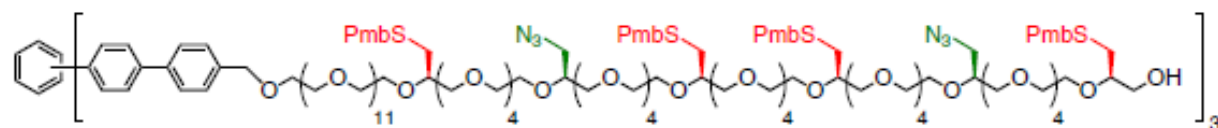
- Monodisperse homopolymers
- Defined monomer sequence polymers
- Oligonucleotides
- Peptides

PEGabet synthesis concept

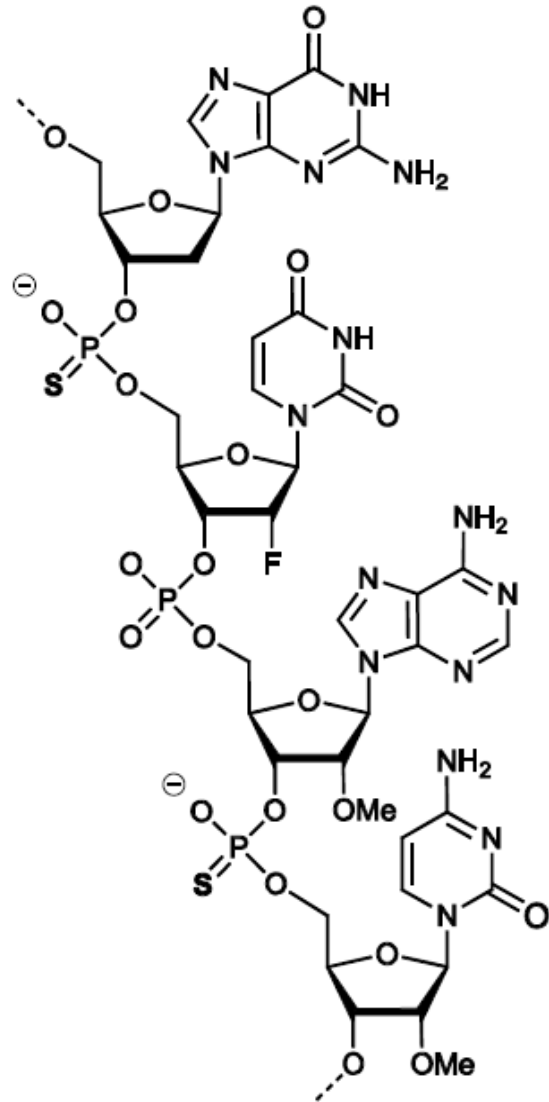




Dong, Liu, Gaffney, Schaepertoens,
 Marchetti, Williams, Livingston
 (2019) **Nature Chem.** Vol 11
 pp136-145.

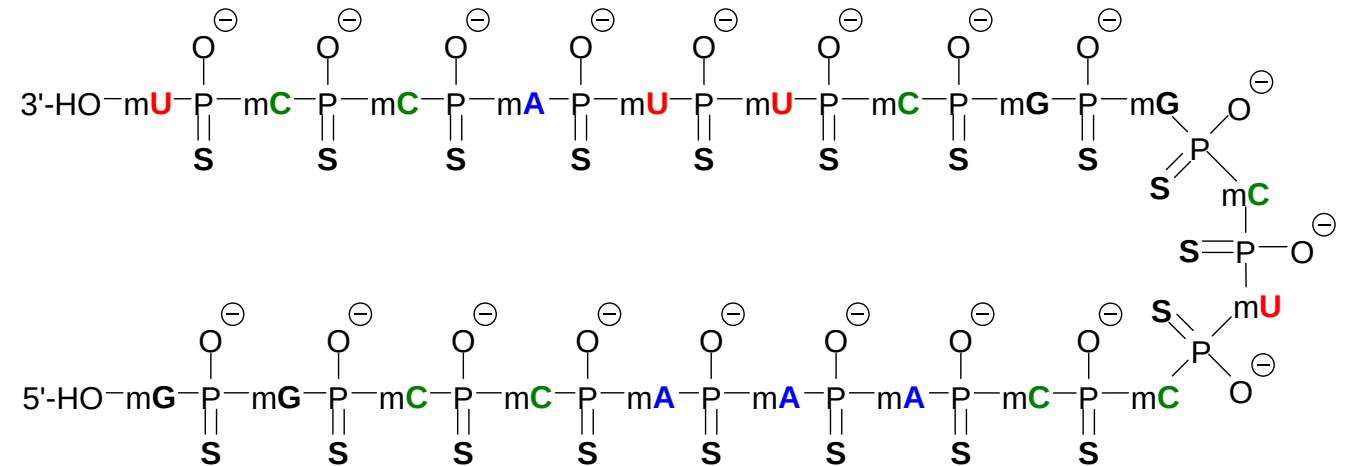


Oligonucleotide Therapeutics



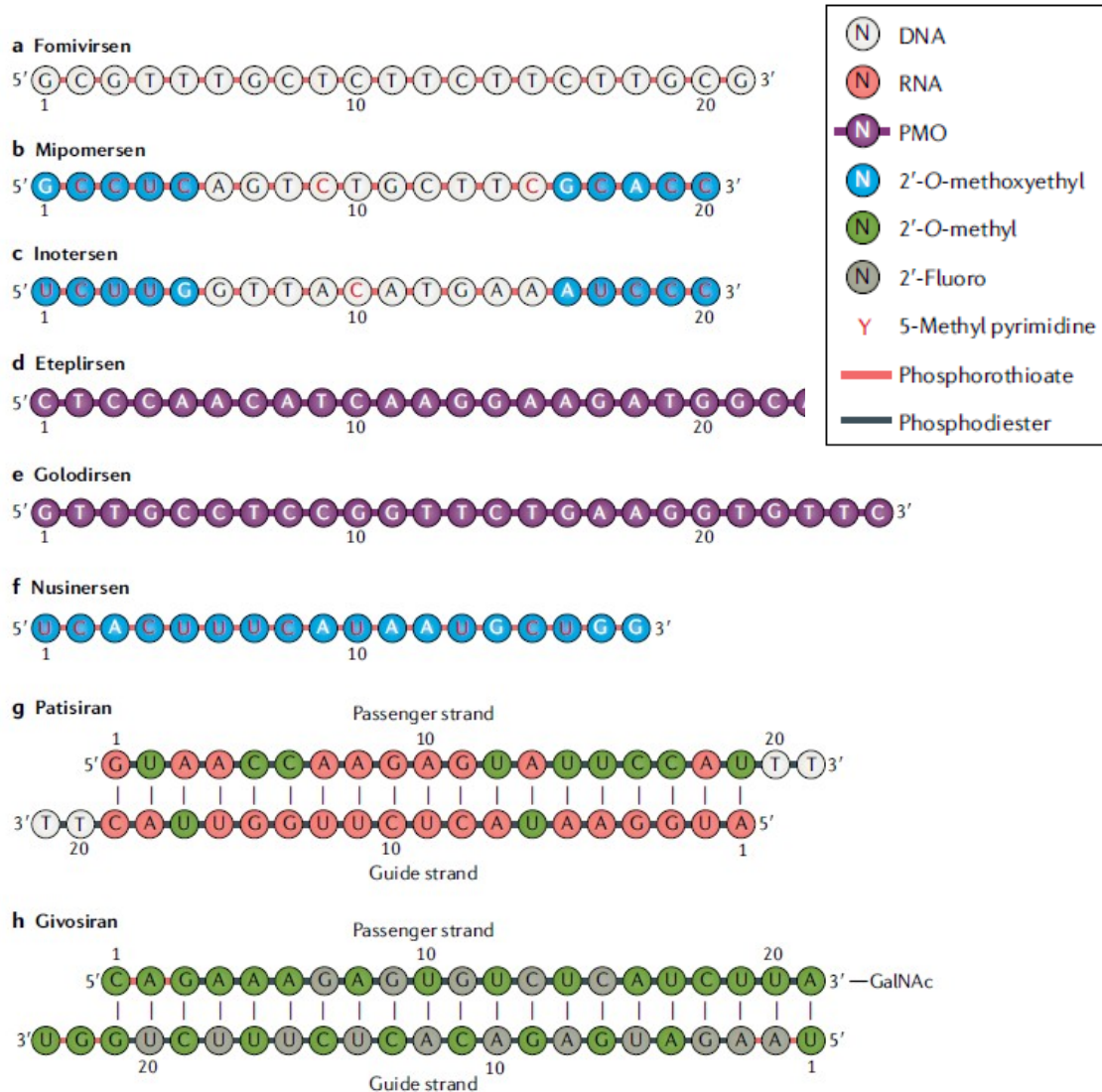
Target: 20-Mer Anti-sense Oligo (ASO)

M23D anti-sense oligo: Lu QL *et al.*, *PNAS*, **2005**, 102, 198.



Modified Oligonucleotides

Oligonucleotide Therapeutics



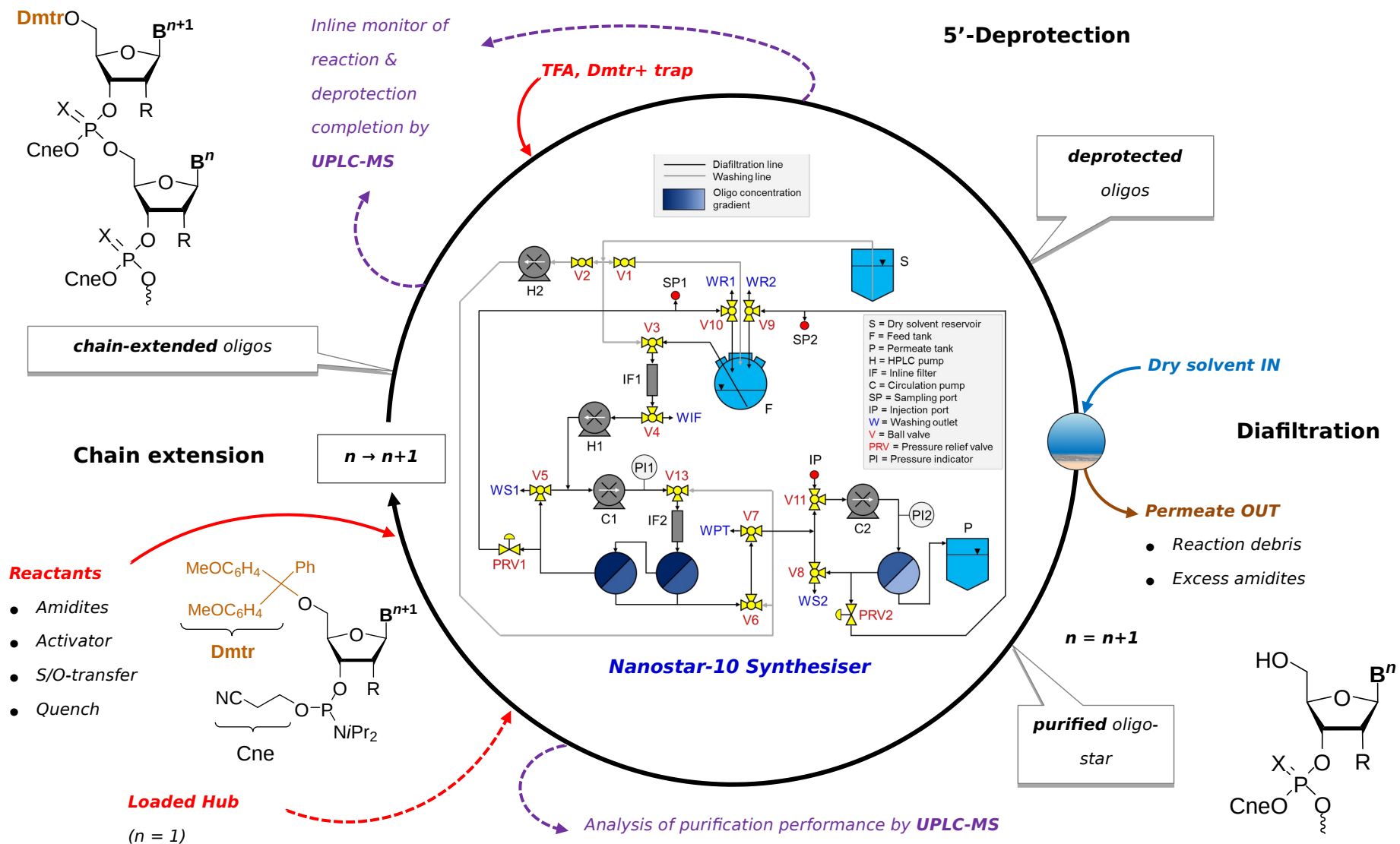
Use of modified nucleic acid fragments, typically 15-25 bases long, to modulate gene expression

Potential modes of action

- ✓ **1.** Interfere with protein expression
- ✓ **2.** Immune system modification
- The number of approved oligonucleotide therapies has grown from 6 at the end of 2017 to 10 at the close of 2020.
- It is estimated that the market for oligonucleotide synthesis will reach €2Bn in 2020, and is growing at 10% CAGR
- More than 150 oligo drugs currently in trials

Exact monomer sequence is critical!

Nanostar-1 Synthesiser (10-20 g 20mer ASO)



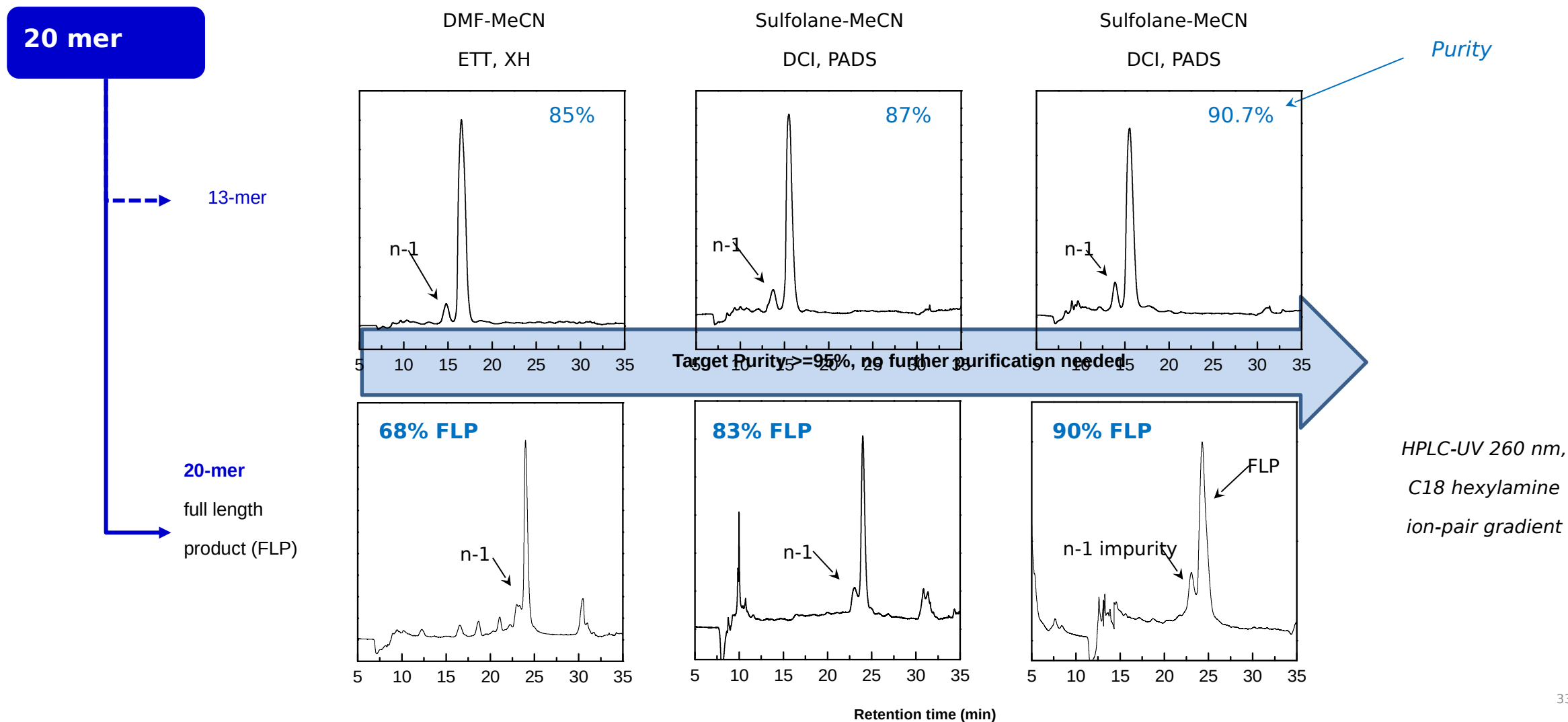
Nanostar-1 Synthesiser

B = ABz, GiBu, CAC, U

R = OMe, F

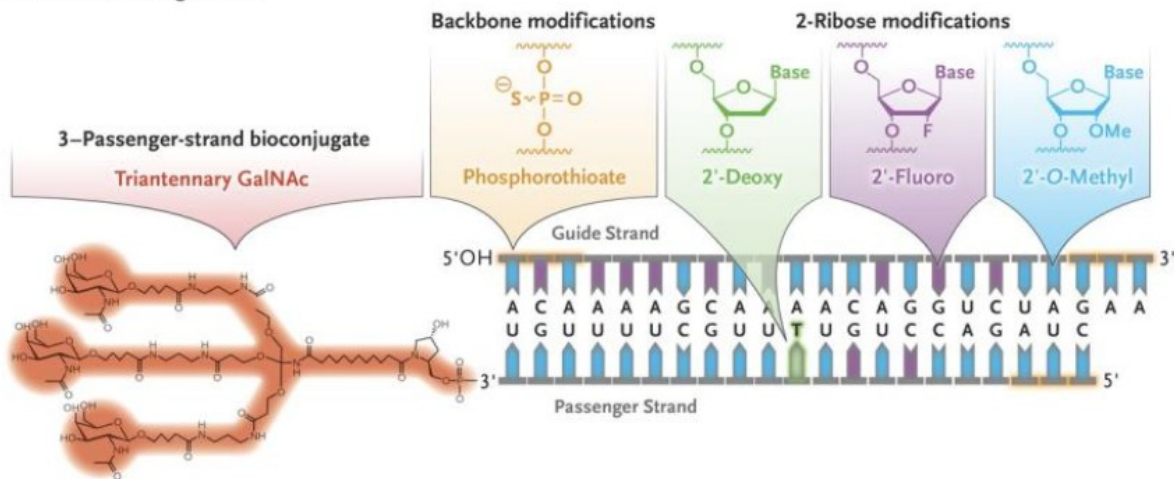
X = O, S

Purity of cleaved and deprotected crude product



Inclisiran

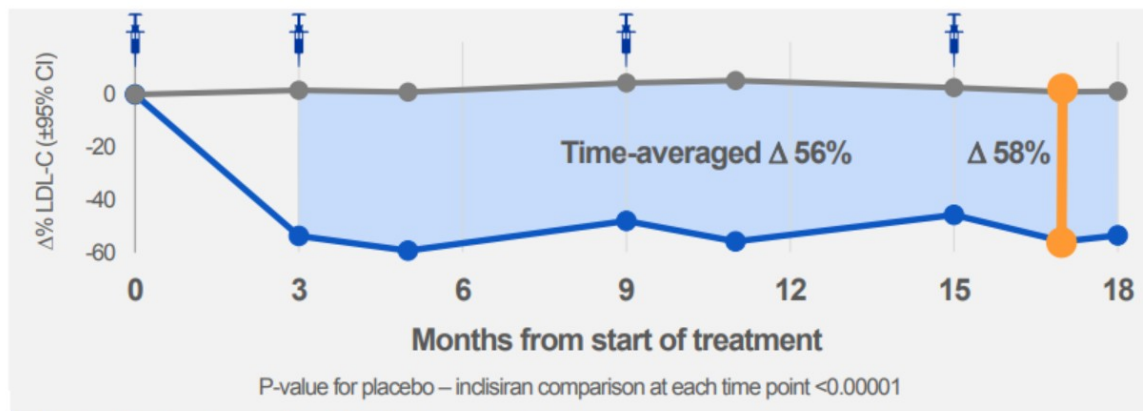
A Chemical Configuration



ORION-10: Efficacy
Durable and potent with consistent effect over 18 months



Percent change in LDL-C over time – observed values in ITT patients



1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points



Our Company ▾ Our Focus ▾ Our Impact ▾



Novartis new analysis further shows durable and potent LDL-C reduction with inclisiran, an investigational first-in-class siRNA cholesterol-lowering treatment

Inclisiran and InNovAZ

Up until now, all licensed oligo drugs are for rare diseases, small patient population, and need only a few 10's to 100's kg drug substance/year

Inclisiran (Novartis) – RNAi drug; outstanding results for reduction of LDL cholesterol implicated in cardiovascular disease. Requires two injections per year versus current multiple pills daily (statins).

Inclisiran – potential for a large patient population....but how to manufacture at this scale?

December 2020 – Exactmer enters development programme with Novartis, AstraZeneca and CPI to develop nanostar sieving for multi-ton production under GMP by 2023

<https://www.uk-cpi.com/news/uk-collaboration-leads-the-way-on-revolutionising-oligonucleotide-medicines-manufacturing>



A Viable Route to Multi-Ton Oligo Manufacturing

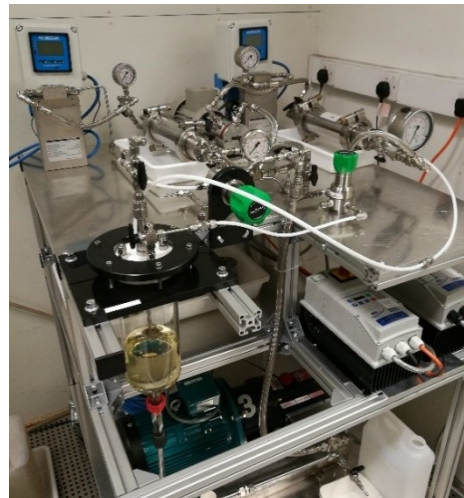
- Scale-up Strategy

Nanostar-10



- Lab scale
- 10-20 g batches
- Flat-sheet membrane cells

Nanostar-100



- Pilot scale
- 100 g batches
- Membrane modules

Larger Plants



Larger plants based on standard chemical reactors combined with skid mounted membrane units

Membranes for Molecular Separations

Thank you for listening and thanks to....

Imperial College
London



ExxonMobil



AstraZeneca

NOVARTIS

Acknowledgements



