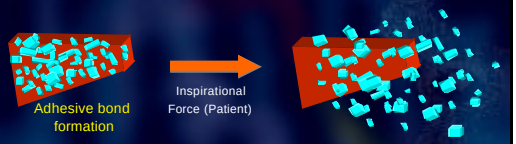
Pharmaceutical Surface Science: A potential way forward!



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Synopsis

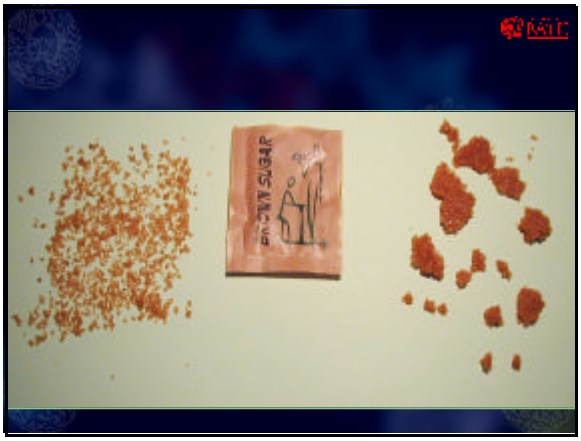
- Introduction
- AFM Studies
  - Adhesion Force Measurements
  - Characterisation of Amorphous domains
  - Surface Stability of Amorphous domains
- Conclusions
- Acknowledgments

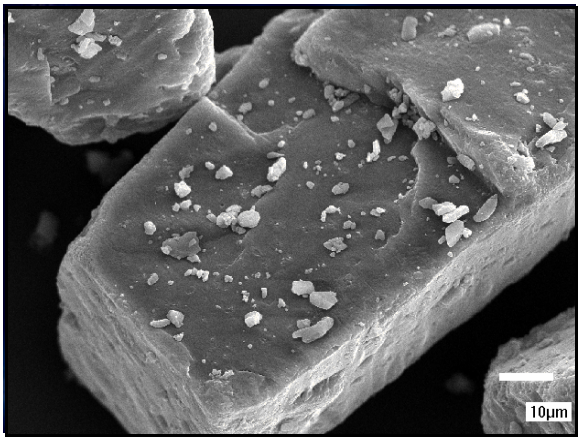
Why is surface characterisation important?

- Pharmaceutical processes involve interfacial contact.
- A change in surface nature will affect interfacial interactions.
- The success or failure of a formulation is dependant on the nature of the surfaces.

What influences the surface properties of powders?

- Presence of different crystal habits
- A change in polymorphic form
- Presence of amorphous material





Colloid interactions in air

Particle interactions are primarily dictated by:

I. van der Waals Forces (LW and AB)

II. Electrostatic Forces

III. Capillary Forces

The relative contribution of forces (II.) and (III.) to the total adhesion/cohesion depends on the interacting materials and relative humidity.

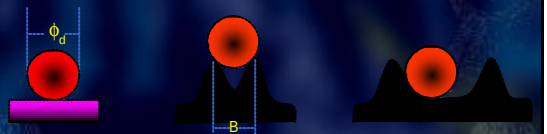
Colloidal Interactions in solution

DLVO Theory
- Lifshitz-van der Waals Interaction
- Electrostatic double layer forces

Extended DLVO Theory
- Lewis acid/base interaction
  - Hydrogen bonding
  - Hydrophobic interaction
- Steric interaction
  - Entropic contribution
  - Osmotic contribution

Additional factors that influence particle adhesion

Surface Energy	-	Intrinsic "free" energy
Surface Roughness	-	Contact Area
Mechanical Properties	-	Hardness
Environmental Conditions	-	Temp. & %RH

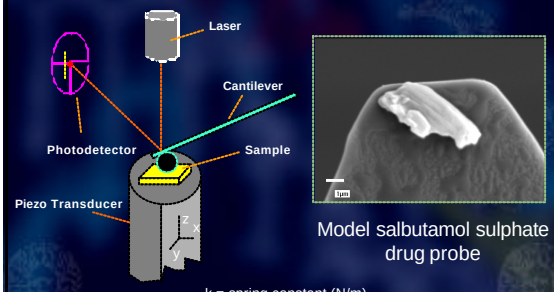


i. Smooth Surface

ii. ϕ_d > B

iii. ϕ_d < B

Atomic Force Microscope (AFM)

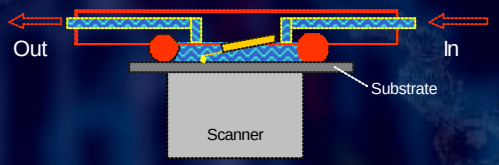


Model salbutamol sulphate drug probe

$F = kdx$

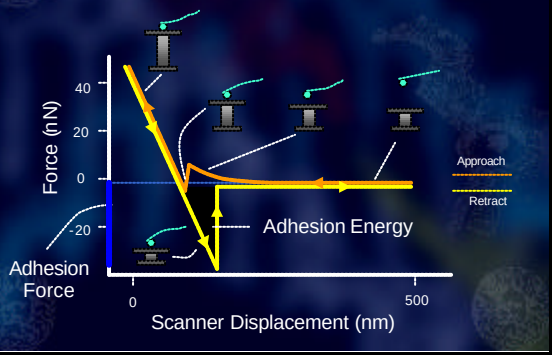
k = spring constant (N/m)
dx = cantilever deflection

In-situ AFM set-up

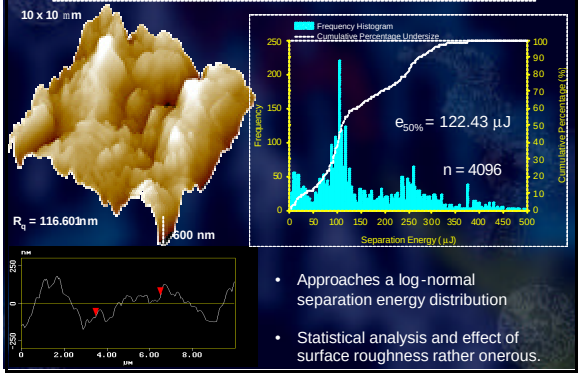


- Hermetically sealed system.
- Potential for high vapour pressure propellant studies.
- Forces and surface stability measurements.

Anatomy of a Force Curve

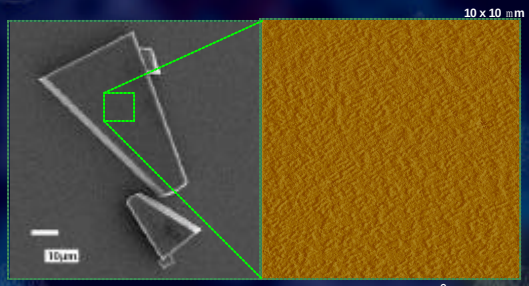


Commercial Grade Lactose



- Approaches a log-normal separation energy distribution
- Statistical analysis and effect of surface roughness rather onerous.

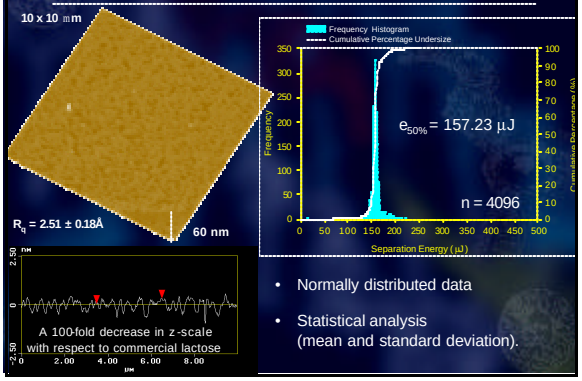
Modified α-lactose surfaces



dominant {0$\bar{1}$1} face

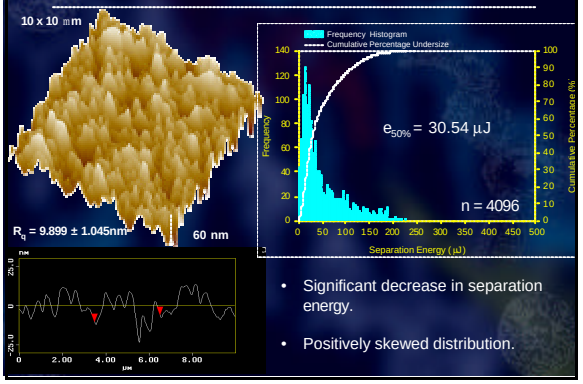
R_q = 2.51Å

Atomically Smooth Lactose



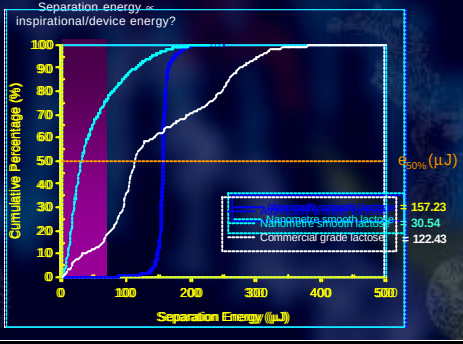
- Normally distributed data
- Statistical analysis (mean and standard deviation).

Nanometre smooth Lactose



- Significant decrease in separation energy.
- Positively skewed distribution.

The role of surface roughness on particle adhesion

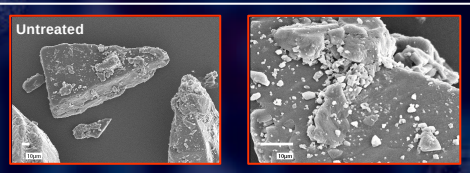


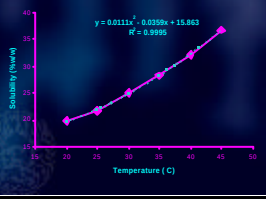
Conclusion (1)

- AFM provides a fundamental insight into the microscopic interactions which govern bulk properties of a DPI formulation.
- Variation in exipient surface roughness at the nanometre-Ångstrom scale dramatically influences drug-lactose interactions.
- Controlling surface roughness of excipient surfaces may lead to increased fine particle delivery.

Can the surface roughness of commercial grade lactose be controllably modified?

UoB surface engineered Lactose

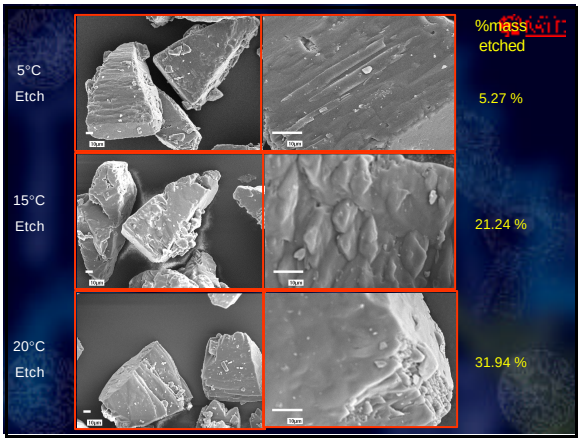




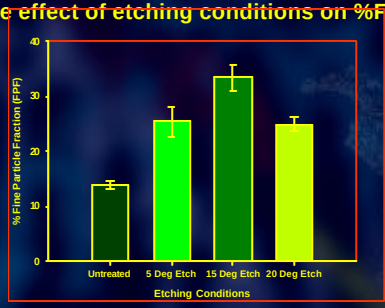
$$\%\sigma_{under} = -\frac{C_T - C_S}{C_S} \times 100$$

$$\%M_{etched} = -\frac{C_T - C_S}{M_{added}} \times 100$$

Patent Pending

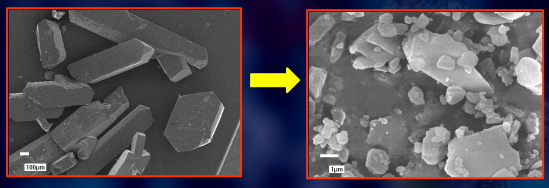


The effect of etching conditions on %FPF



- Salbutamol Sulphate:Lactose (1 : 67.5 %w/w) blend
- In vitro apparatus: TSI @ 60 L/min (cut-off d_{ae} = 6.4μm).
- Cyclohaler device (n = 10)

Crystalline vs. Processed



Generation of Amorphous regions

- Thermodynamically metastable
- Physico-chemical instability
- Irreversible changes to a formulation

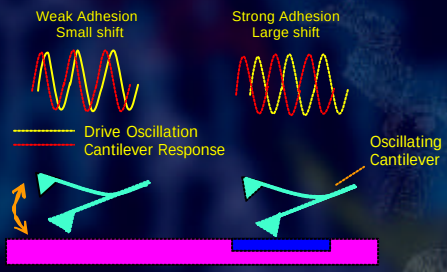
Is a few % amorphous content important?

If all at the surface!

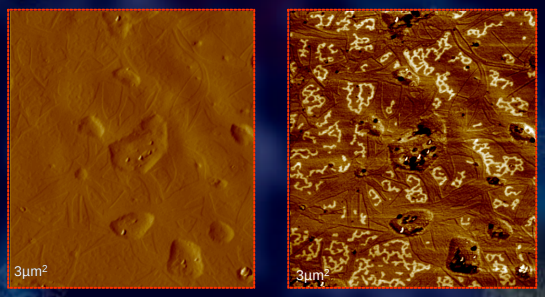
- Altered interfacial interactions
- Change in product properties
- Batch-to-batch variation

How do we measure the nature of processed powder surfaces?

Phase Imaging

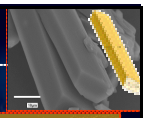


Cross section of a Starch particle

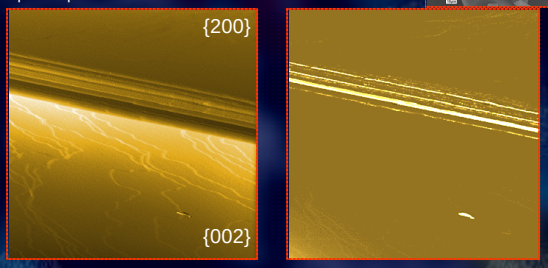


Amplitude Phase

Salbutamol Sulphate Crystal



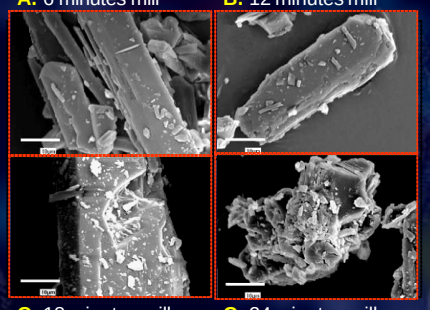
5µm x 5µm



Topography Phase

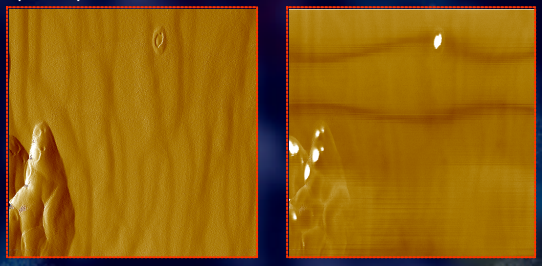
0° 100°

Processed material



Processed salbutamol sulphate crystal

1µm x 1µm



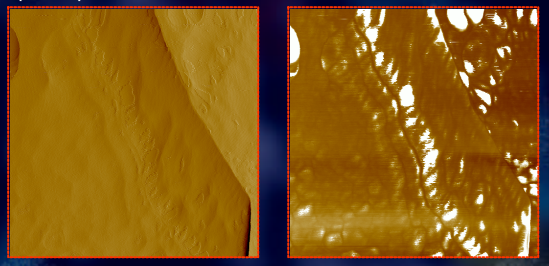
Topography Phase

6 minutes milling

0° 100°

Processed salbutamol sulphate crystal

1µm x 1µm



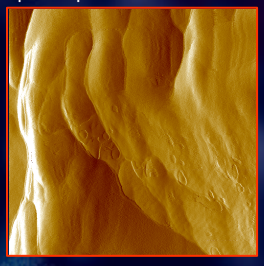
Topography Phase

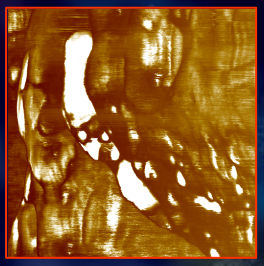
12 minutes milling

0° 100°

Processed salbutamol sulphate crystal

1µm x 1µm





Topography

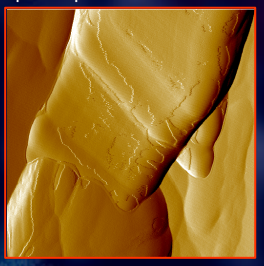
Phase

18 minutes milling

0° 100°

Processed salbutamol sulphate crystal

1µm x 1µm



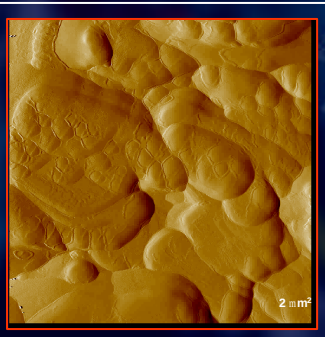
Topography

Phase

24 minutes milling

0° 100°

Amorphous mobility

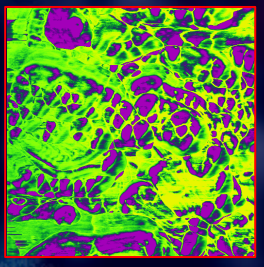


45% RH

Micronised particle surface

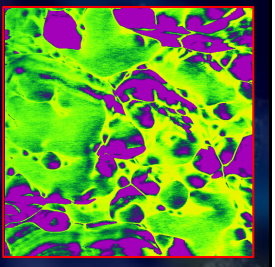
Ostwald ripening?

2 x 2 µm



t = 0 min

2 x 2 µm

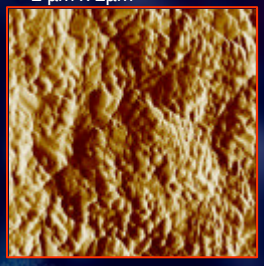


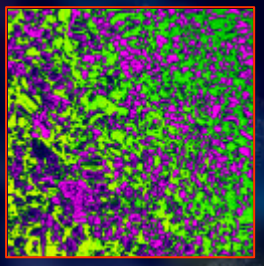
t = 30 min

0° 100°

Metastable Surface

2 µm x 2µm





Topography

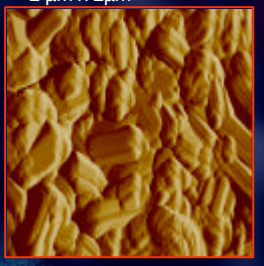
Phase

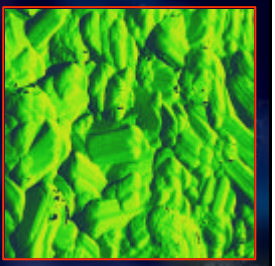
Micronised particle (30%RH)

0° 100°

Surface Reconstruction

2 µm x 2µm





Topography

Phase

Micronised particle (65 %RH)

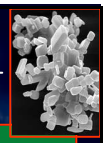
0° 100°

Conclusion

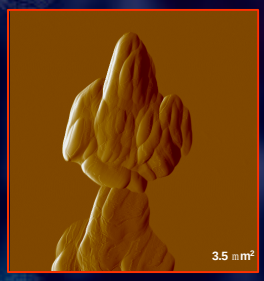
- The presence and molecular mobility of amorphous regions will adversely affect the stability and characteristics of a DPI formulation.
- Development of new methodologies are required in the conditioning and processing of inhalation drug products

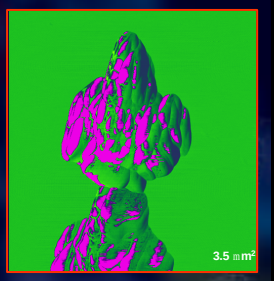
SEDS: A potential long term solution ?

SEDS produced Salbutamol Sulphate



SEDS produced Salbutamol Sulphate

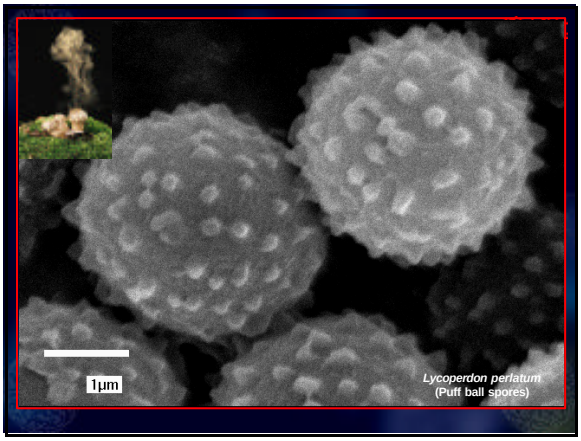


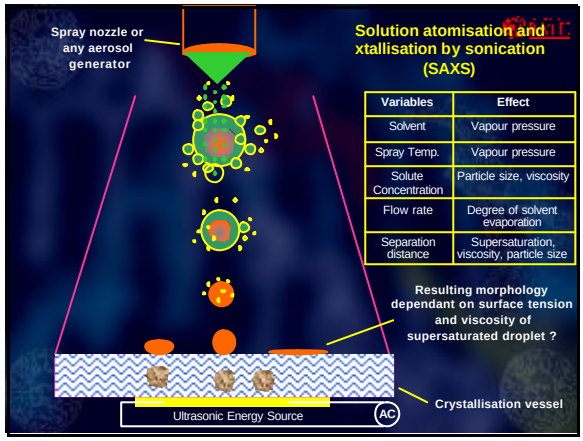


Interfacial interactions and stability may remain an issue ?

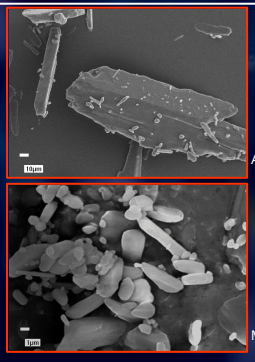
Constructive particle production wish-list

- High purity micron sized particles
- Defined morphological structures (spherical preferred)
- Defined surface structure (nanometre asperities)
- Single step operation with a dial-up particle size input
- Physico-chemical stable particles
- Controlled physico-chemical properties (surface energy)





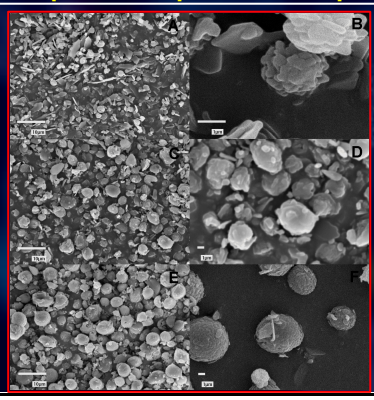
Conventionally processed material



As supplied Paracetemol

Micronised Paracetemol

SAXS produced paracetemol particles

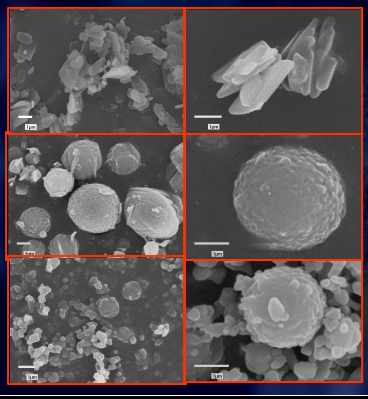


1% w/w

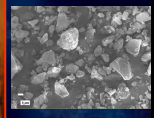
5% w/w

10% w/w

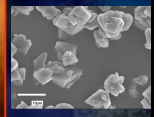
Ethanol 5.8 kPa / Methanol 12.3 kPa / Acetone 24.0 kPa



Stability of micronised and SAXS produced budesonide particles in a HFA pMDI



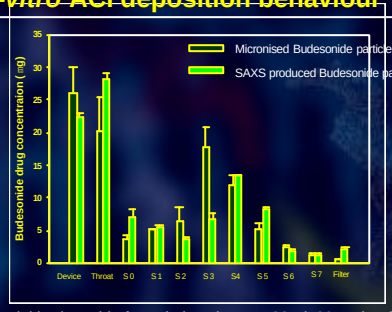
Micronised Budesonide



SAXS produced Budesonide

Extended dispersion testing

in-vitro ACI deposition behaviour



- Model budesonide formulations in HFA-227 (100µg dose)
- In vitro apparatus: ACI @ 28.3 L/min
- No significant difference in %FPF and Delivered Dose

General Conclusions

The AFM can be used, in real time, to characterise:

- Adhesive characteristics of particulate materials.
- Physical transformations on particle surfaces.
- Thermodynamically metastable amorphous domains, at a nanometre level.
- Long term stability of the powdered systems.

General Conclusions

- In combination with bulk techniques, AFM may potentially play a pivotal role in the design and modifications of DPI and suspension based formulations.
- There is a further need to correlate:
  - Relationship between surface thermodynamics (contact angles, IGC), force measurements (AFM, CPD) and *in vitro* performance.
  - Macroscopic properties of surfaces and mesoscale properties of interfacial interactions and related adhesion.

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Dr. Stephen Edge
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100µm