Enabling a Healthier World

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Simultaneous spray drying for innovative dry powder inhaler combination formulations

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Lonza, Bend, OR

22 June 2022

Business Use Only

Addressing Market Challenges as One

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Four Key Trends:

1. More Complex, Highly Potent Molecules

- **>250** highly complex molecules in pipeline
- Using pioneering methodologies to navigate challenges, and advance

2. Small Biotechs Driving Innovation

- Our division is geared toward small biotechs
- Represent **60%** of our customer base
- Driving novel development

3. Accelerated Timelines to Market

- Dedicated to taking customers to market faster
- Specialist fixed-time and cost pathways
- Early Phase and beyond

4. Uncertain In-market Demand

- Customers require flexibility through to commercial production
- Flexibility is our top contractual priority

>70%
of New Drug Approvals are on an Accelerated Pathway

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You Only Need One CDMO

Being global puts a team of connected experts from Small Molecules in your time zone and by your side.

3 Regions

6 Sites

22 June 2022

Outline

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01

Intro to particle engineering for inhalation delivery

02

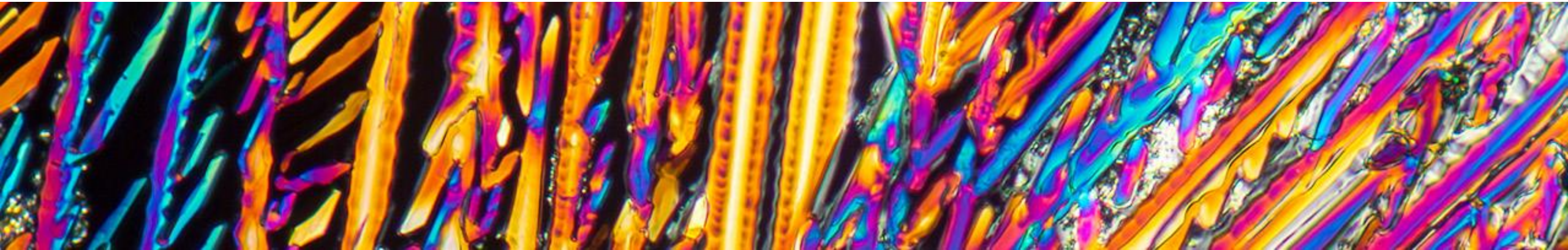
Motivation for improved lung cancer therapies

03

Case study 1:
Bevacizumab monotherapy

04

Case study 2:
Beva/small molecule simul-spray combo therapies



Particle engineering for lung delivery

Aerodynamic diameter is key

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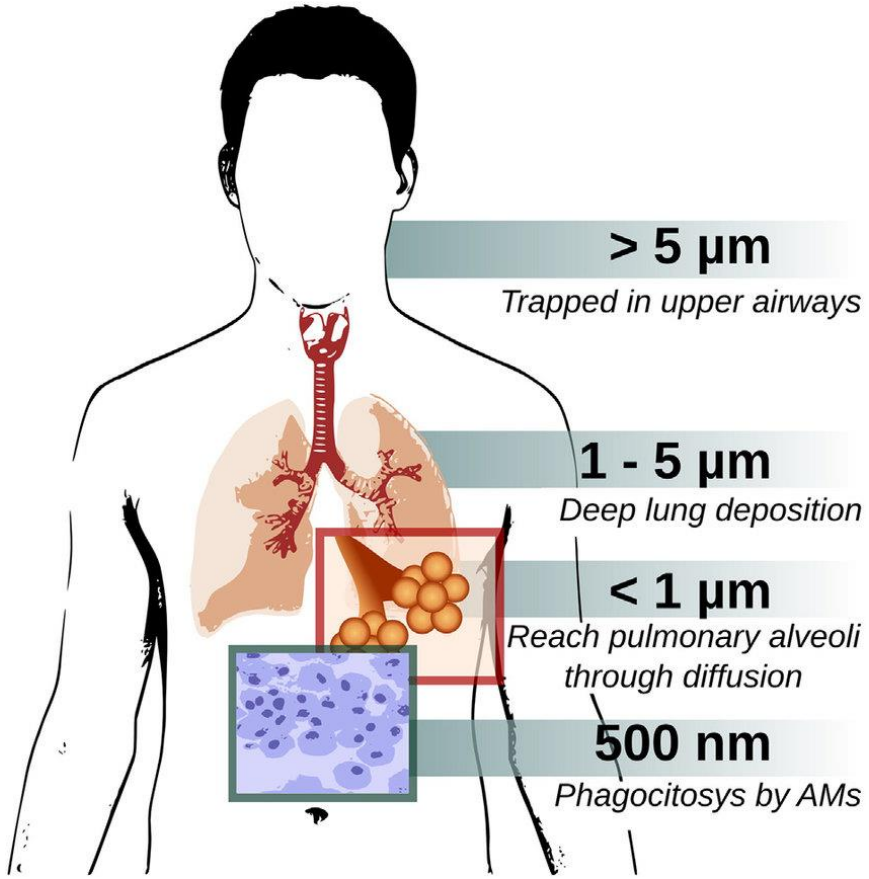

Costa et al Adv Drug Deliv. Rev 2016

- The lung is designed to keep particles out, so we must work to ensure good delivery.
- Particle diameter and density are therefore critical to product performance
- Aerodynamic diameter is used to determine how a particle will behave in the respiratory tract

$$d_a = d_e \left(\frac{\rho_p}{\rho_0 \chi} \right)^{\frac{1}{2}}$$

- ρ_0 is reference density of 1000kg/m^3,
- chi is shape factor (1 for spheres)

Spray drying enables dry powder inhaled formulations

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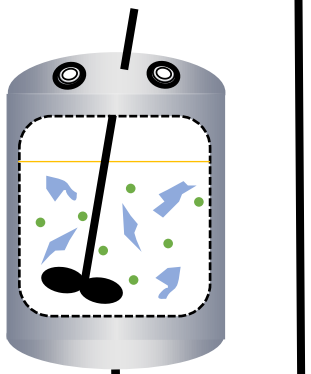
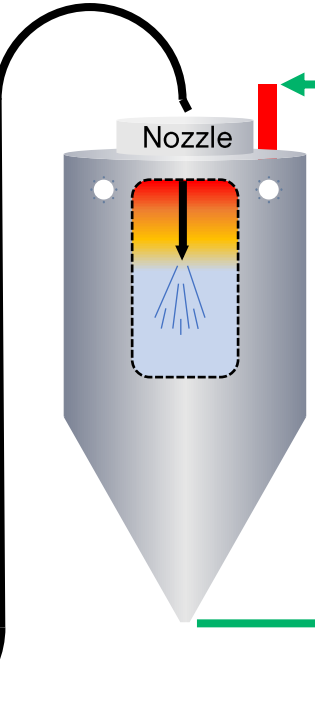
FEED SOLUTION

Drug is dissolved with excipients in a common volatile solvent.



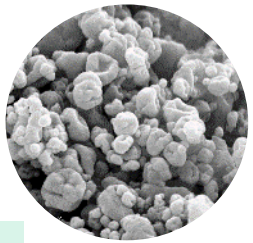


DRYING GAS

Minimal exposure to high temperature due to evaporative cooling

DRYING CHAMBER

Solvent rapidly evaporates from atomized droplets to form amorphous powder particles



POWDER COLLECTION

The resulting SDD powder is separated from the gas stream using a cyclone and collected

Spray drying of large & small molecules is well-precedented

- Spray drying small molecules common for oral bioavailability enhancement
- 20+ compounds at Lonza Bend: mAbs, fAbs, DNA, oligonucleotides, VLPs, peptides

Minimize API degradation

- Evaporative cooling limits heat exposure
- Use of stabilizing excipients like trehalose
- Shear exposure controlled by pump & atomizer choice

Tunable particle engineering

- Atomization conditions
- Solution composition
- Drying kinetics
- Customized solutions for challenging particle collection

Strong need for improved lung cancer treatments

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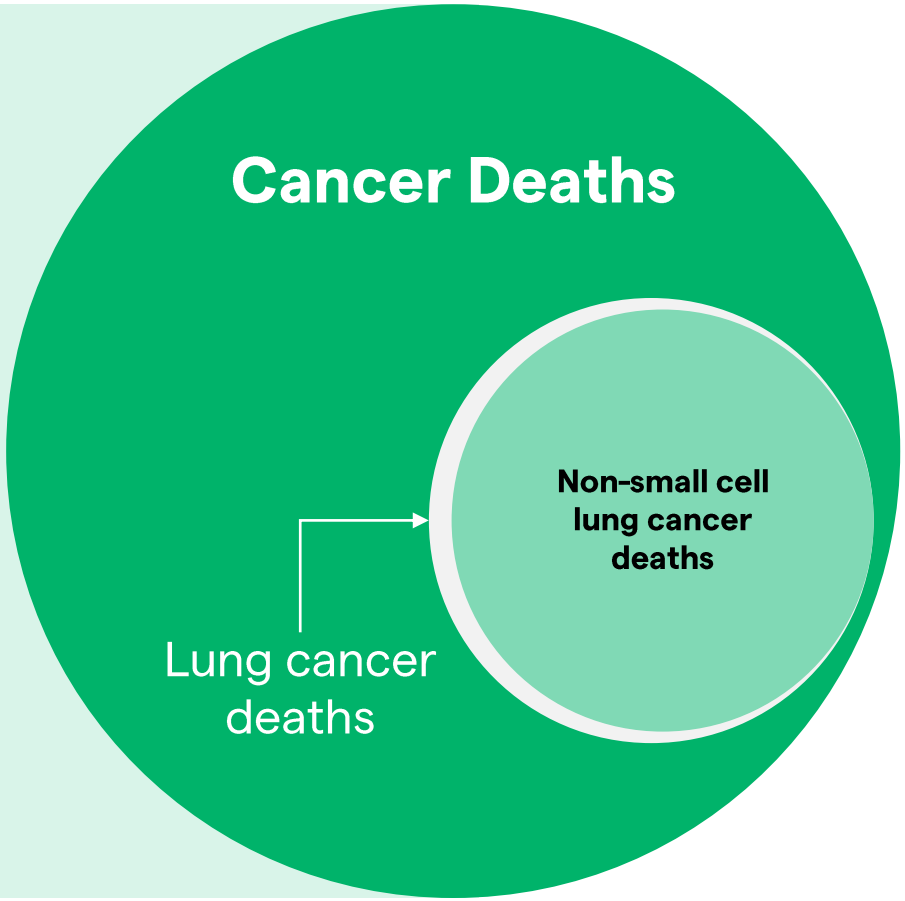
Lung cancer is the leading cause of cancer-related deaths in the US and worldwide. 25% of US cancer deaths

90% of lung cancer mortality is due to Non-Small Cell Lung Cancer (NSCLC)

Advanced cases of NSCLC have a five-year survival rate of ~5%



Areas approximately to scale

Late-stage lung cancer treatment examples: all systemic

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Chemotherapy	Cisplatin	Carboplatin	Paclitaxel	Docetaxel	*Topotecan*
Immunotherapy	Pembrolizumab	Atezolizumab	Nivolumab	Nivolumab +ipilimumab	
Other targets	VEGF (bevacizumab, ramucirumab etc.)	EGFR (erlotinib, gefitinib, etc.)	ALK-inhibitors (alectinib, crizotinib, ceritinib, lorlatinib, etc.)		

Black text: IV infusion

Green Text: Oral administration

Advantages of local therapy for lung cancer

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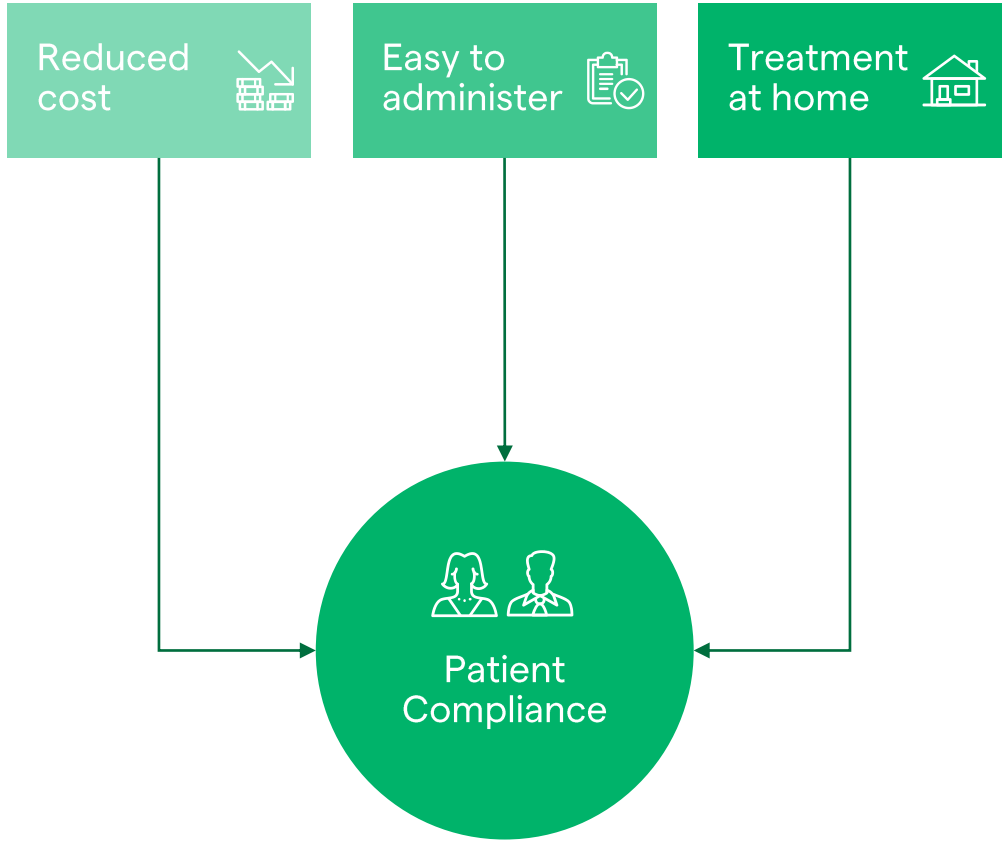
Improved therapeutic outcomes

Challenge	Effectiveness limited by toxicity and side effects at high dose
Solution	Reduce systemic dose by lung delivery to affected tissues
Challenge	Poor exposure in lung tissue due to metabolism or distribution issues
Solution	Local administration circumvents first-pass metabolism and the need for distribution to the tissues from systemic circulation

Better patient experience



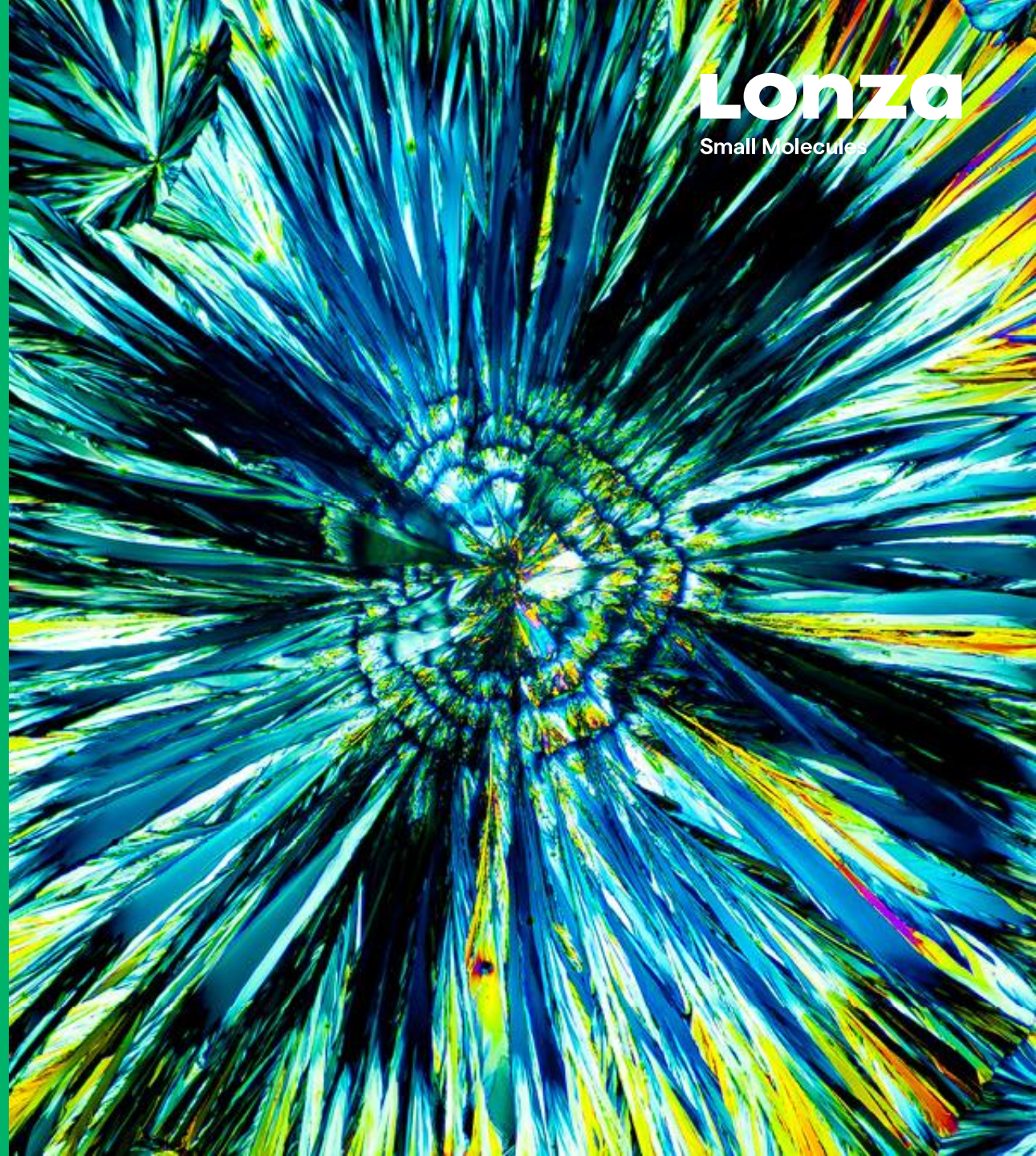
Case study 1:

Inhaled bevacizumab dry powder monotherapy

Open access peer-reviewed study now published in AAPS PharmSciTech (2021)

“Local treatment of non-small cell lung cancer with a spray-dried bevacizumab formulation”

22 June 2022



Meet the model compound: bevacizumab

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- Indications: NSCLC, colon cancer, glioblastoma, etc.
- Approved in 2004 as Avastin®, biosimilars Mvasi® and Zirabev® now on the market

Bevacizumab for NSCLC Stage III+

1. Inhibits VEGF angiogenesis pathway, reducing tumor's ability to grow
2. Primary treatment in combination with chemotherapy
3. Maintenance treatment on its own after chemo is no longer tolerated. IV infusion every 3 weeks.
4. Risk of severe bleeding leads to substantial exclusion of patients who could benefit from therapy

Avastin® is a registered trademark of Genentech, Inc.
Mvasi® is a registered trademark of Amgen, Inc.
Zirabev® is a registered trademark of Pfizer, Inc.

Delivery of mAb therapies for lung indications

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Standard of Care

- mAbs for lung diseases are delivered as sub-Q injections or IV infusions
- Most are recurring treatments, weekly or monthly

Challenges

- Systemic administration is not always ideal
- Invasive delivery
- Expensive in-clinic administration
- Patient compliance for recurring treatments

Local Delivery Alternative: Nebulizer

1. Pre-clinical evidence nebulizers are effective for pulmonary delivery of some mAbs
   (Respaud et al Exp Opin Drug Deliv 2015)
2. Self-administered at home
3. Physical stability concerns for liquid formulations
4. Treatments take minutes-hours, not seconds

Would formulation as a dry powder inhaler be possible?

Formulation of bevacizumab dry powder by spray drying

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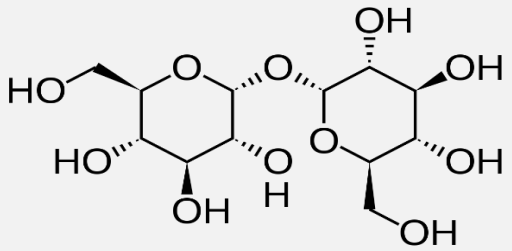
40% active formulation

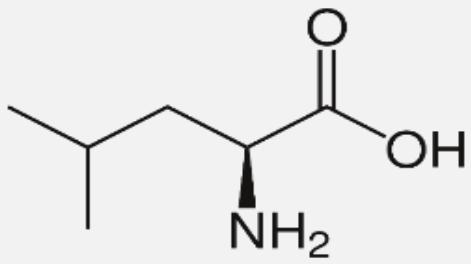
Stable for 12 months at 25°C

High process yield of ~90%



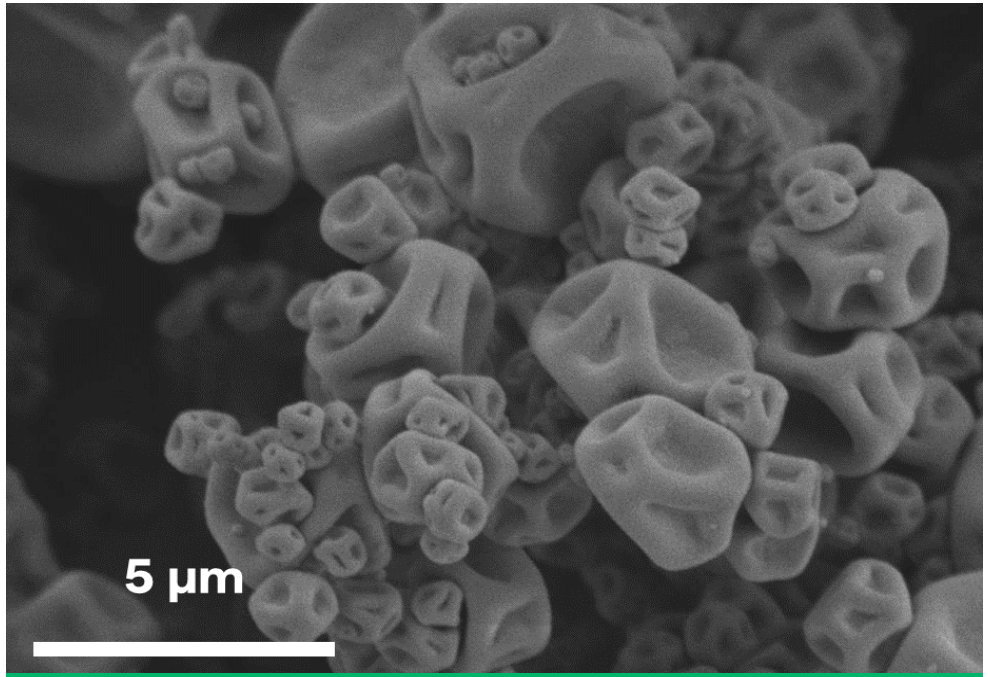
Trehalose

Stabilize amorphous state
Replace H-bonds from water



L-leucine

Crystallizes at surface of particle
Improves aerosol properties
Vehring Pharm Res 2008



SEM image of bevacizumab particles for inhalation

Aerosol properties of bevacizumab SDD

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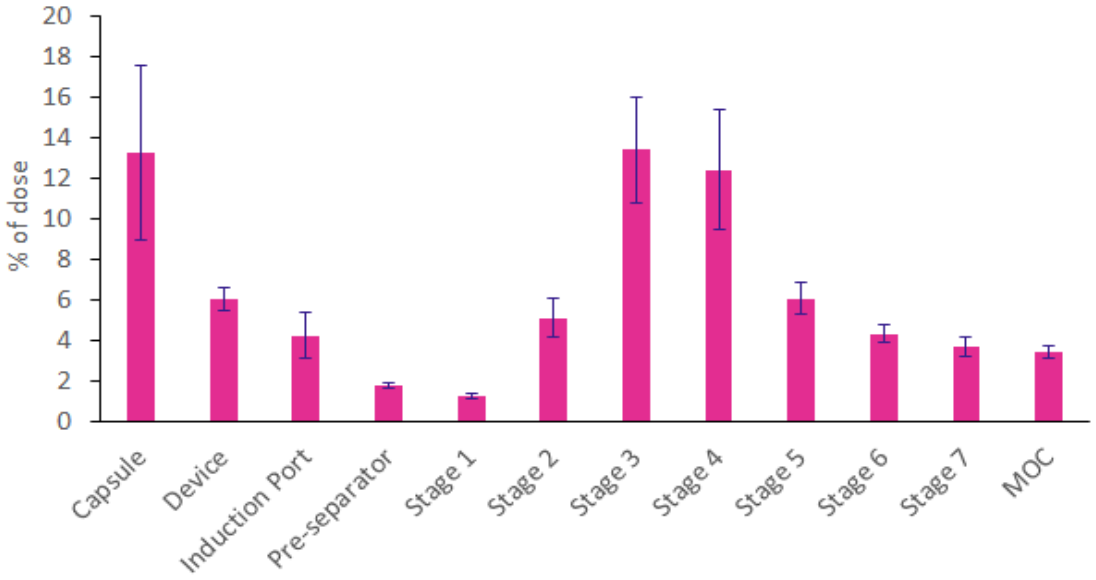
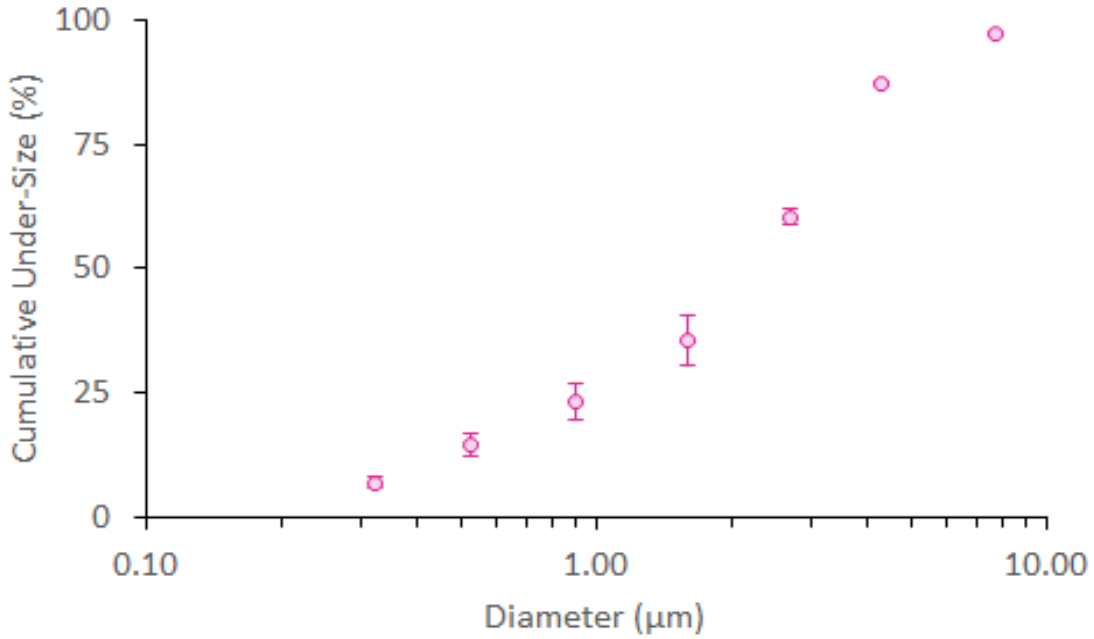
SDD aerodynamic diameter in range for deep lung delivery with high fine particle fraction on NGI





MMAD (µm)	Geom Std Dev	FPF (%) < 5 µm	vFPF (%) < 2.5 µm
2.2	1.9	81	41

Bevacizumab SDD maintains anti-VEGF activity

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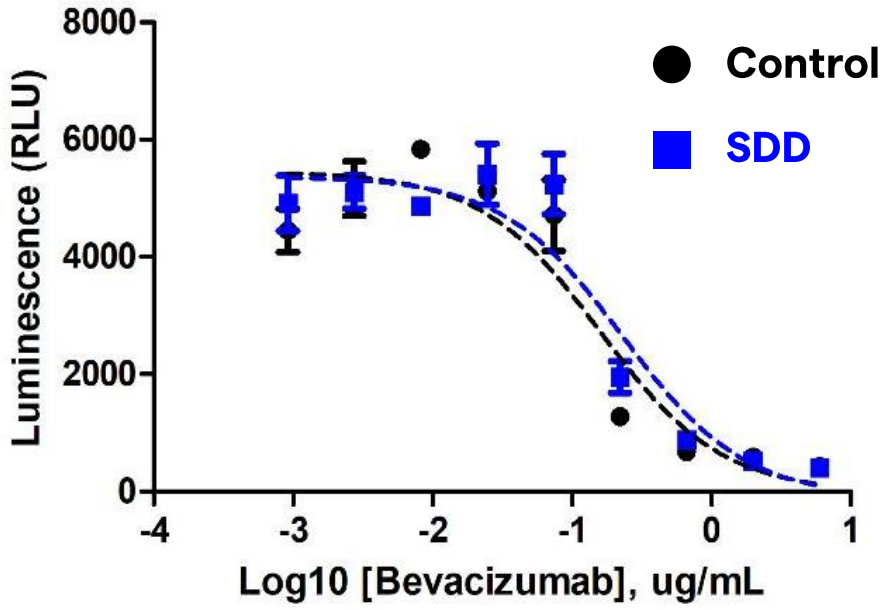
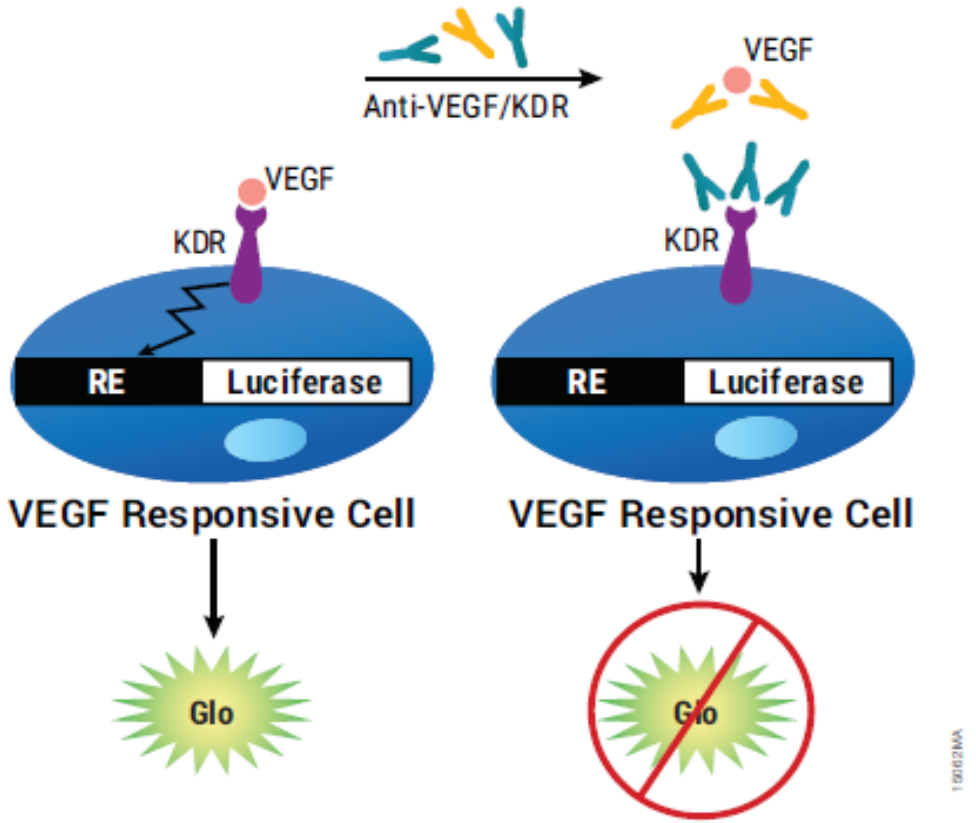
Bevacizumab binds with VEGF as effectively as control over a wide range of concentrations, using luciferase reporter assay kit for VEGF activity





Luciferase reporter assay kit for VEGF from Promega.com

Efficacy study in NSCLC rat model

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1

Efficacy study conducted in orthotopic nude rat NSCLC model in collaboration with Lovelace Biomedical

2

CALU-3 tumor cells were intratracheally instilled into rats' lungs

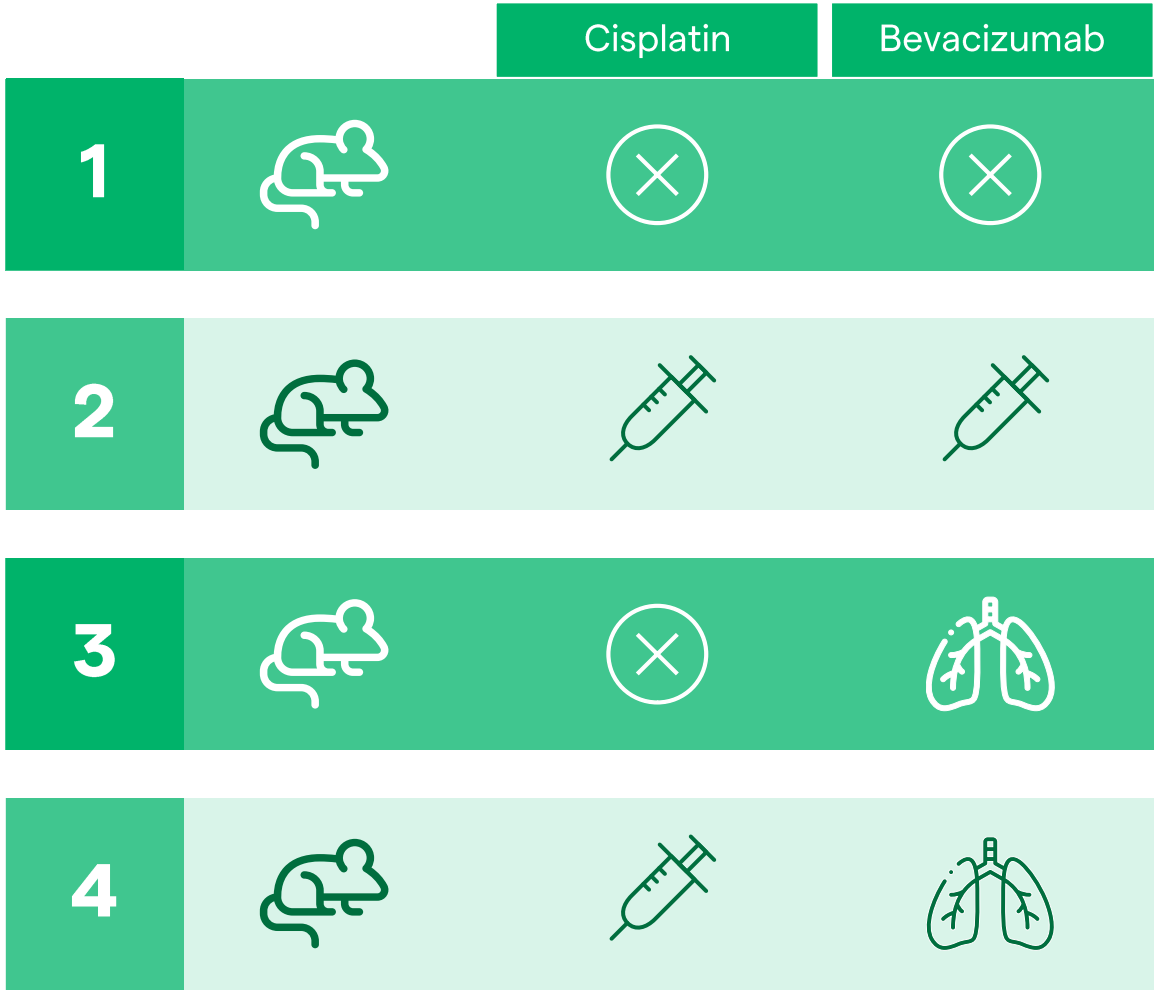
3

Treatment administered weekly from weeks 4-8 after instillation

4

Study endpoint: lung weight (tumor burden)

Group	Cisplatin	Bevacizumab	Animals
1	None	None	15
2	IP 3 mg/kg	IP 15 mg/kg	15
3	None	INH 1.5 mg/kg	15
4	IP 3 mg/kg	INH 1.5 mg/kg	15



Inhaled bevacizumab is efficacious in vivo

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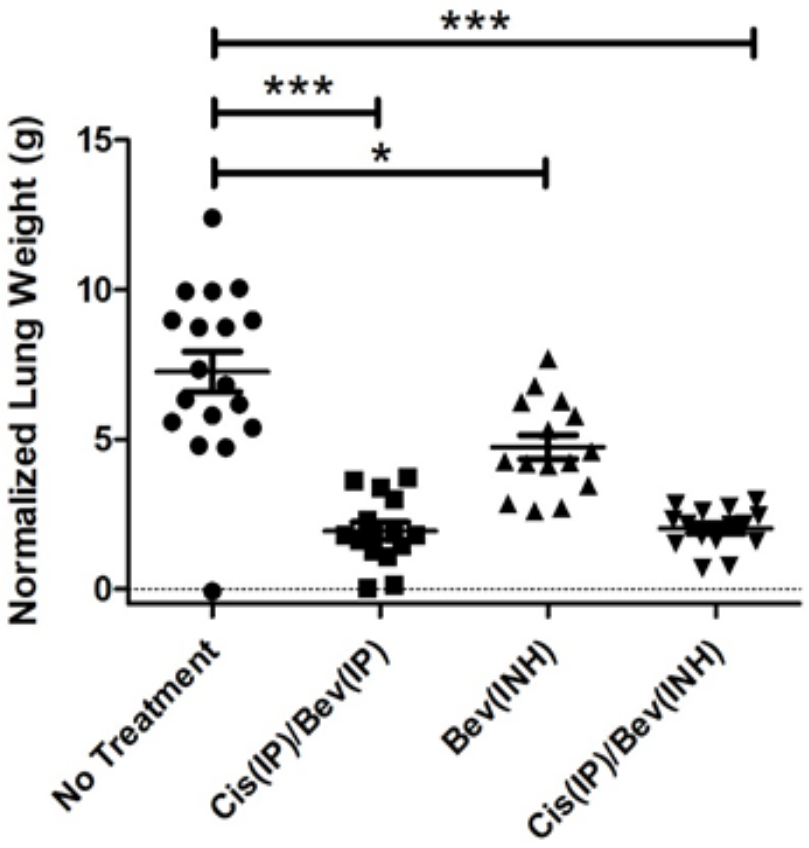

* = p< 0.05, *** = p < 0.0005

Key findings for efficacy

- Inhaled bev + IP cisplatin reduces tumor mass as much as positive control (IP bev + IP cisplatin) At 1/10th the bevacizumab dose
- Inhaled bev alone reduces tumor burden significantly compared with negative control
- Also tested in maintenance study where inhaled bevacizumab prolonged survival after chemo ended

Conclusions for case study 1

A promising future for patients

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Spray drying: A platform for pulmonary delivery

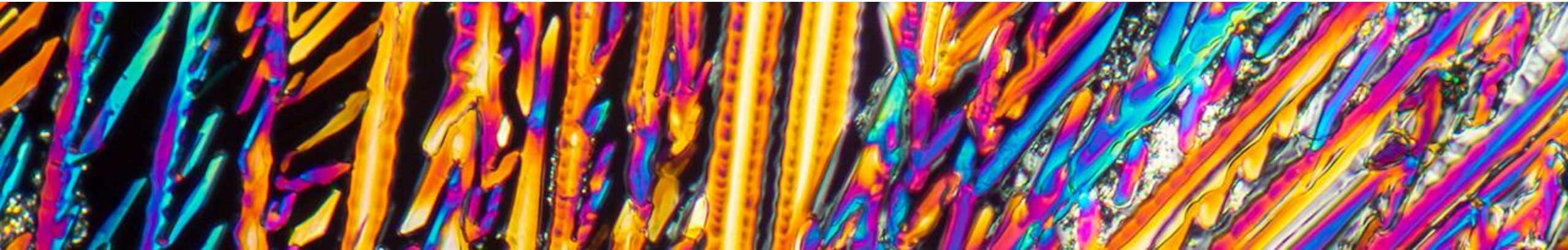
- Spray drying enables scalable particle engineering for inhalation without damaging delicate actives
- Spray dried powders have good aerosol properties, physical stability at ambient temp, and biological activity

Bevacizumab reduces tumor size in rat model of lung cancer

- Bevacizumab was effective at reducing tumor growth in rat model as a primary or maintenance therapy

Improve patient quality of life

- Simple and inexpensive at-home administration when dealing with a challenging disease
- Potential for lower dose and reduced side effects



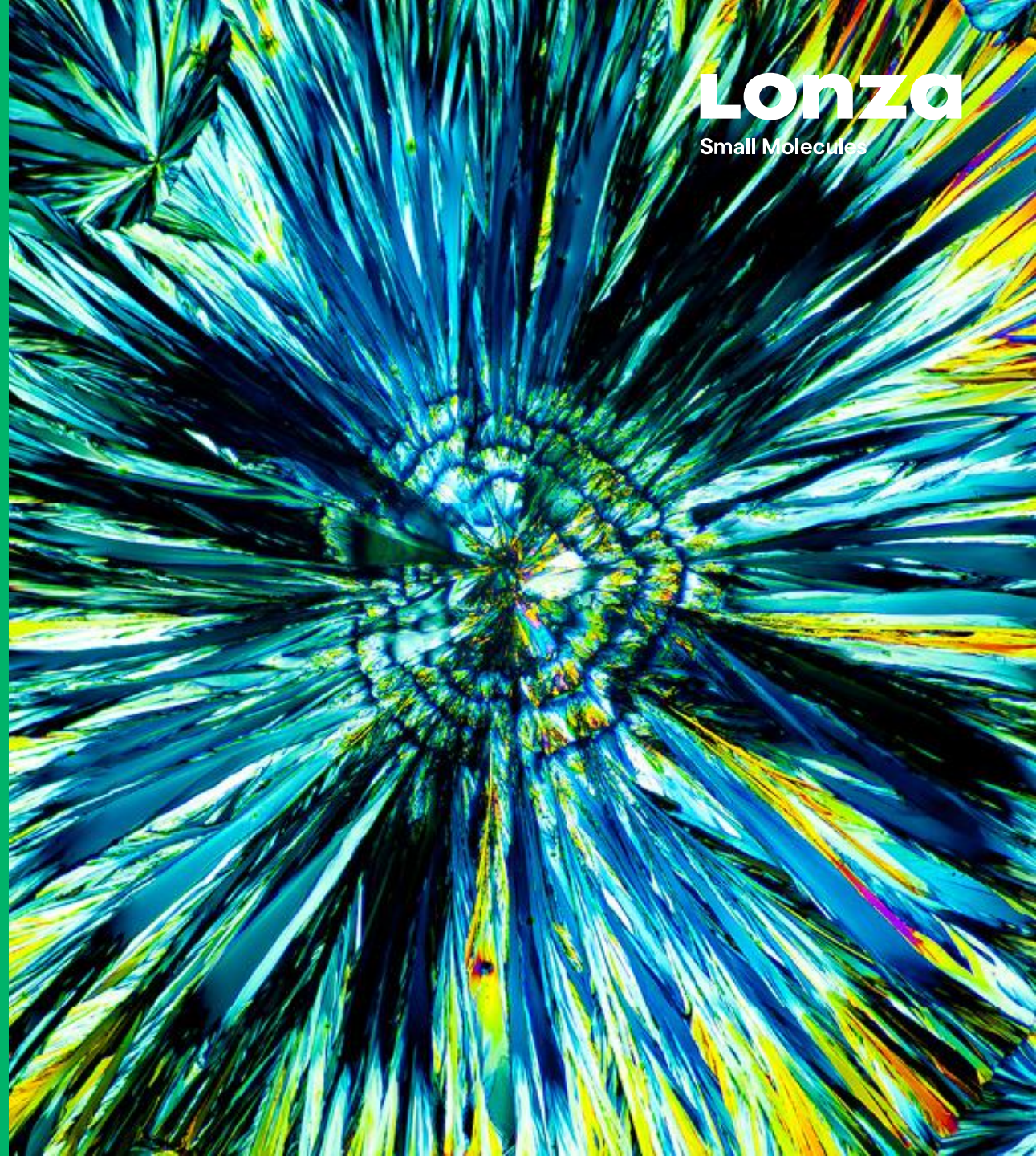
Case study 2:

Simul-spray bevacizumab/ small molecule combination therapy

Open Access peer-reviewed study now published in Pharmaceutics (2022)

“Simultaneous spray drying for combination dry powder inhaler formulations”

22 June 2022



Why combination therapies?

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Combination therapies help patients

Challenge	Adherence is a problem in 70% of patient populations for inhaled treatments
Solution	Lower patient burden by reducing number of medications
Challenge	Medication costs are high for managing lung diseases
Solution	Combination products can reduce overall cost of treatment, particularly for asthma management

Local treatment of lung cancer combination

Challenge	APIs of interest cannot be easily formulated into a single product
Solution	Simul-spray drying circumvents formulation challenges

Simultaneous spray drying

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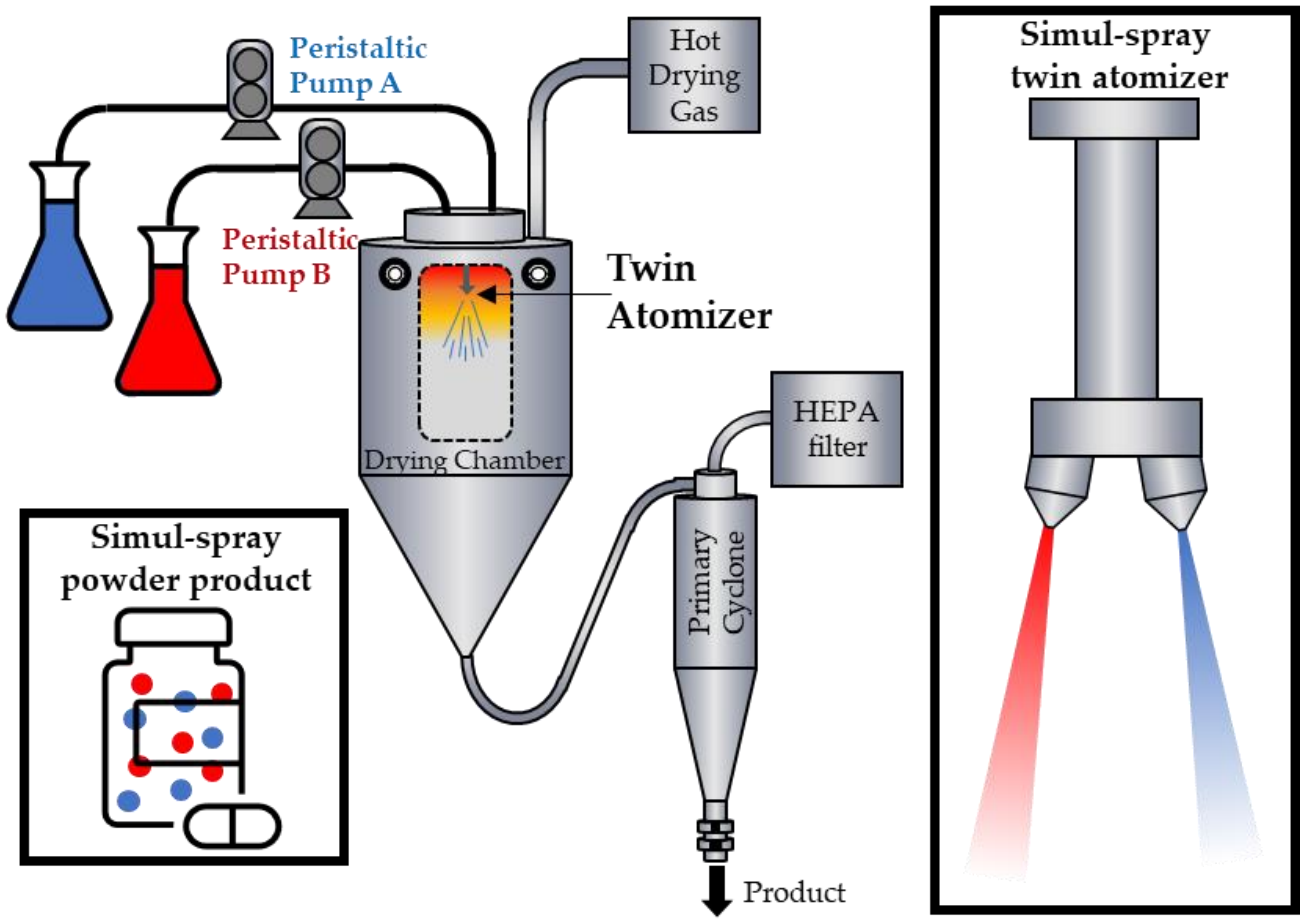
One spray dryer + Two solution feeds = **Simul-spray product**

- Avoid milling/blending
- No need for a common spray solvent between APIs
- No need for a single formulation
- Powder product is intimately blended
- Adjust final powder composition via liquid flow rates
- Can also use one feed as a placebo for easy dose escalation



Model systems and powder composition results

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3 lung cancer-relevant combinations

Beva/Erlotinib

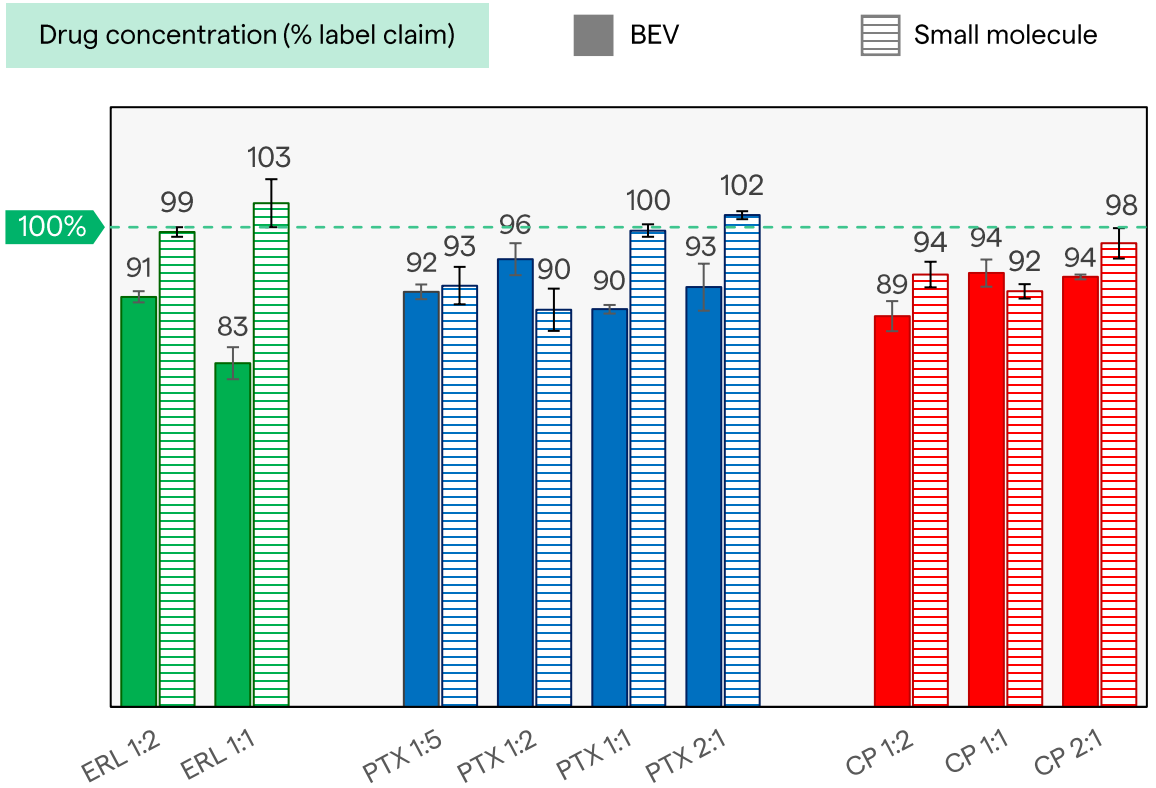
- Erlotinib is an EGFR inhibitor, used when NSCLC has an EGFR mutation
- Erlotinib has low aqueous solubility
- Simul-sprayed 1:2 and 1:1 mass ratios

Beva/Paclitaxel

- Paclitaxel is a chemotherapy
- Also has low aqueous solubility
- Simul-sprayed 1:5, 1:2, 1:1, 2:1 mass ratios

Beva/cisplatin

- Cisplatin is a chemotherapy used in combination with beva as NSCLC standard of care
- Aqueous solution has chemical stability issues
- Simul-sprayed 1:2, 1:1, 2:1 mass ratios



SEM images: Erlotinib bevacizumab simul-spray

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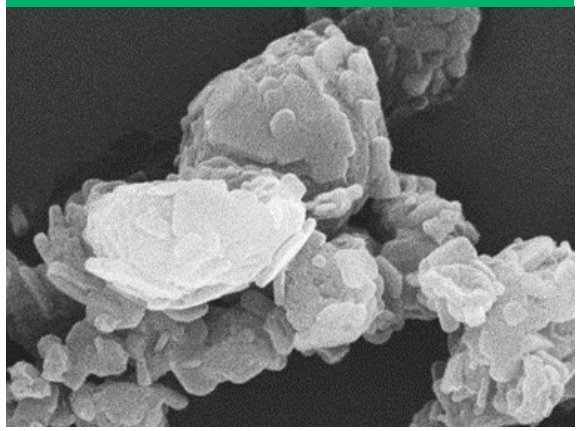
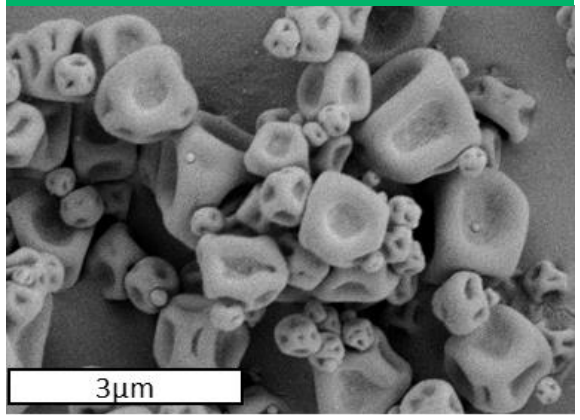
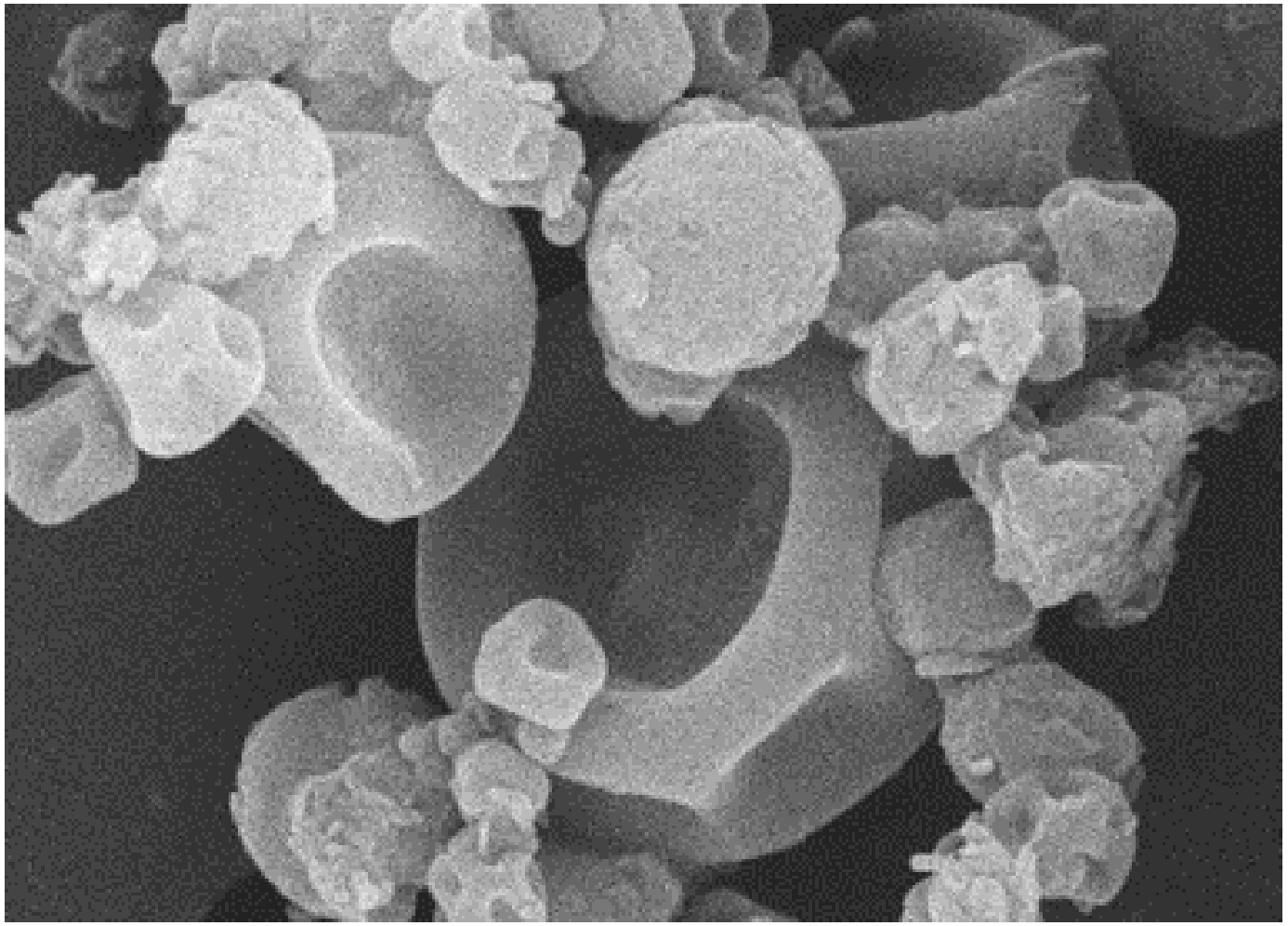
Erlotinib mono



Beva mono





SEM images: Paclitaxel bevacizumab simul-spray

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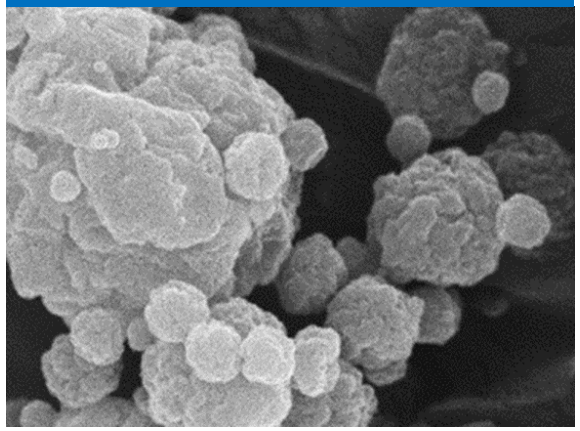
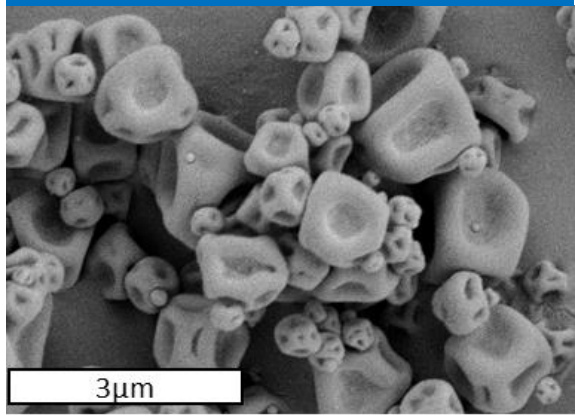
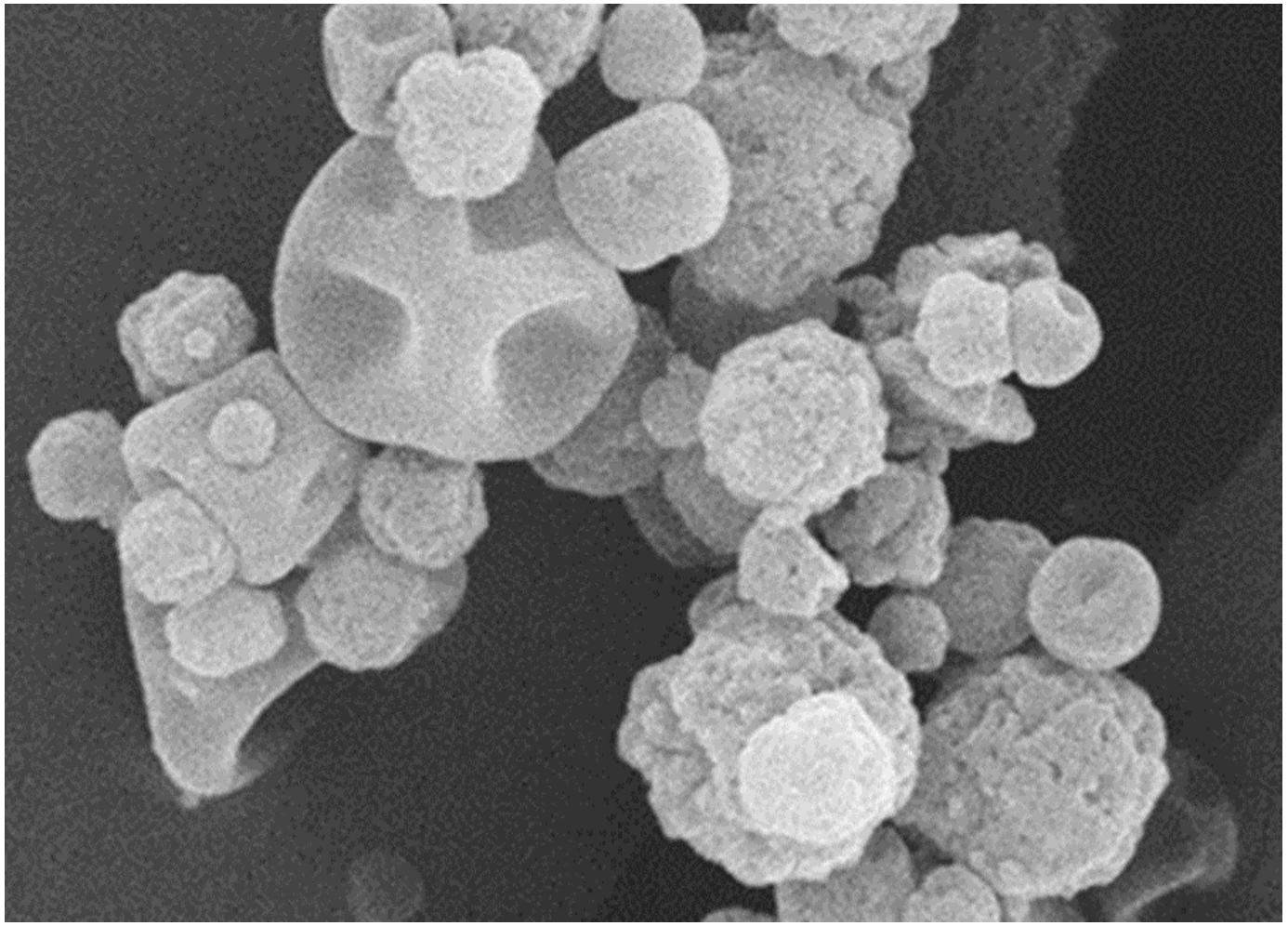
Paclitaxel mono



Beva mono





SEM images: Cisplatin bevacizumab simul-spray

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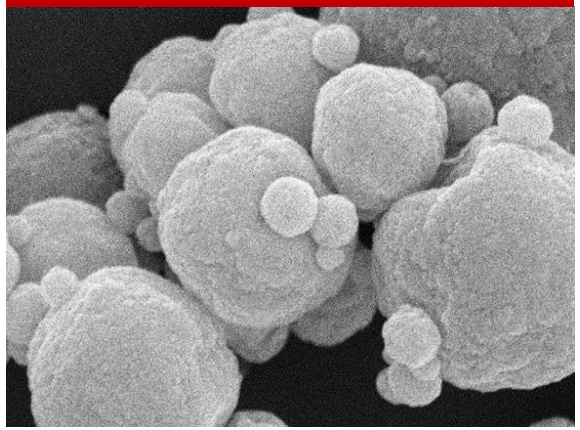
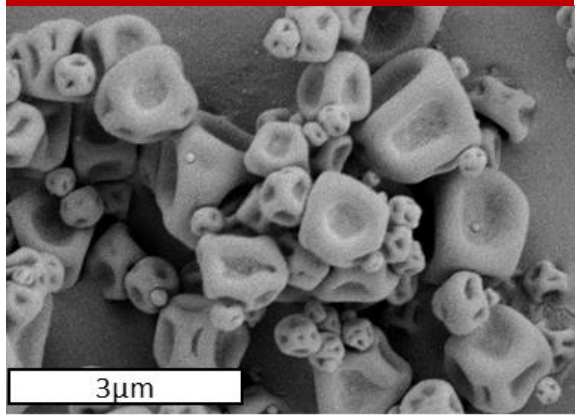
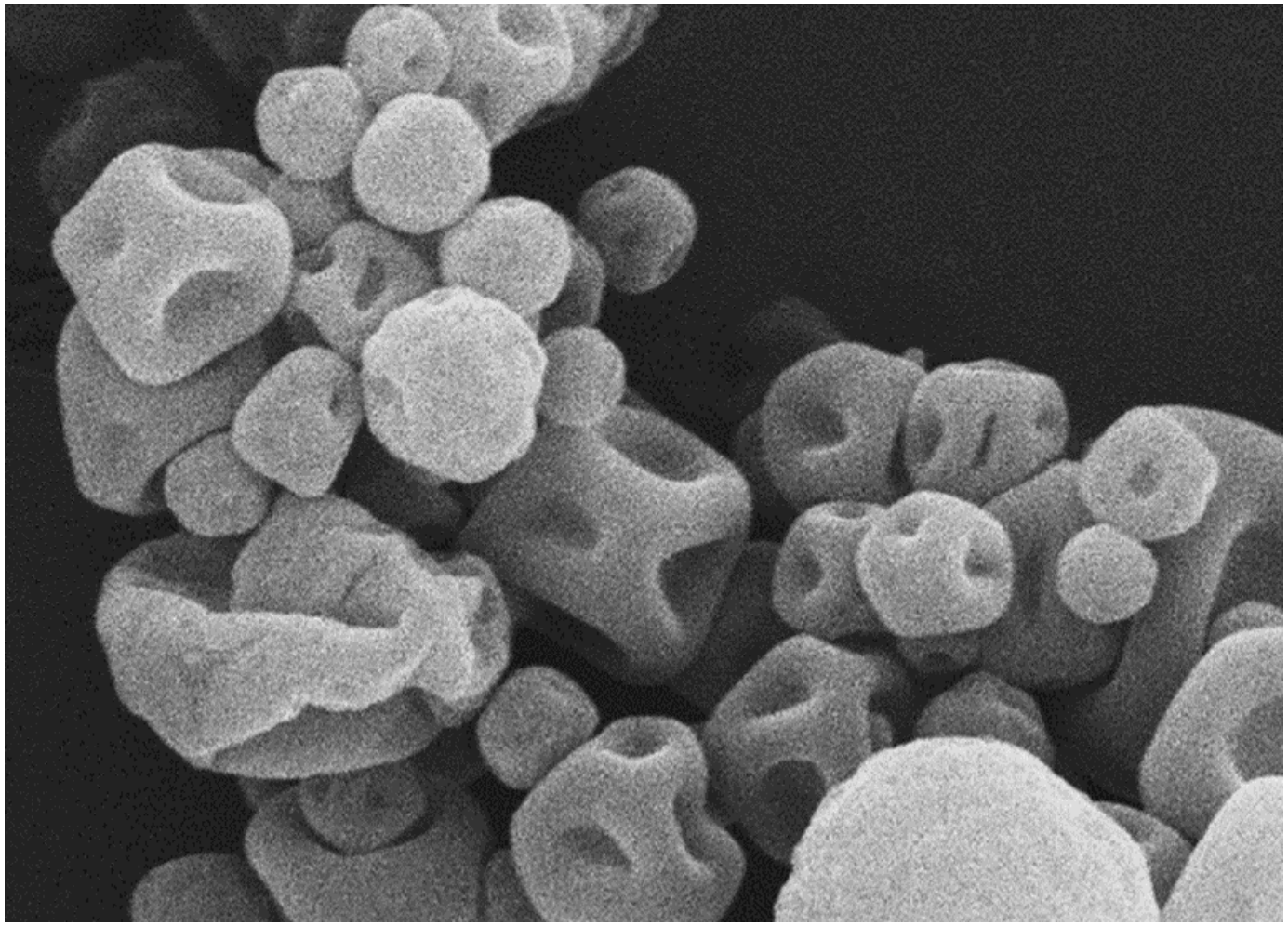
Cisplatin mono



Beva mono





Simul-spray formulations have targeted aerosol properties

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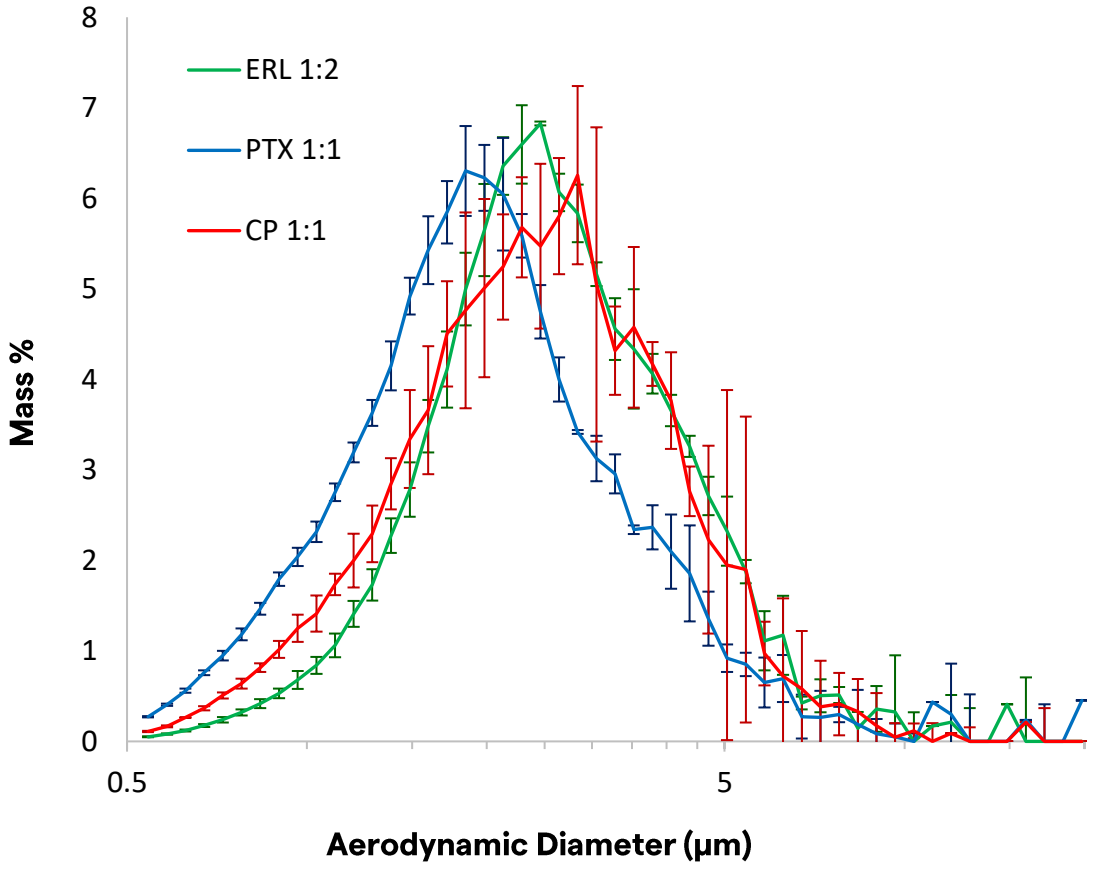
- Mass median aerodynamic diameters for all formulations are < 3 microns, targeted for deep lung delivery
- PTX formulations have highest fine particle dose by fast-screening impactor

Formulation	APS MMAD (µm)	APS GSD (µm)	FSI FPD/ Fill Mass, %
ERL 1:2	2.9	1.7	43.4 ± 2.5
ERL 1:1	2.5	1.7	46.3 ± 1.5
PTX 1:5	2.3	1.6	64.3 ± 8.0
PTX 1:2	2.4	1.7	64.0 ± 0.0
PTX 1:1	2.4	1.7	54.6 ± 7.0
PTX 2:1	1.8	1.7	65.2 ± 5.9
CP 1:2	2.8	1.7	58.0 ± 0.7
CP 1:1	2.7	1.7	57.7 ± 1.6
CP 2:1	2.7	1.7	59.9 ± 2.7



Simul-spray formulations retain bevacizumab's activity

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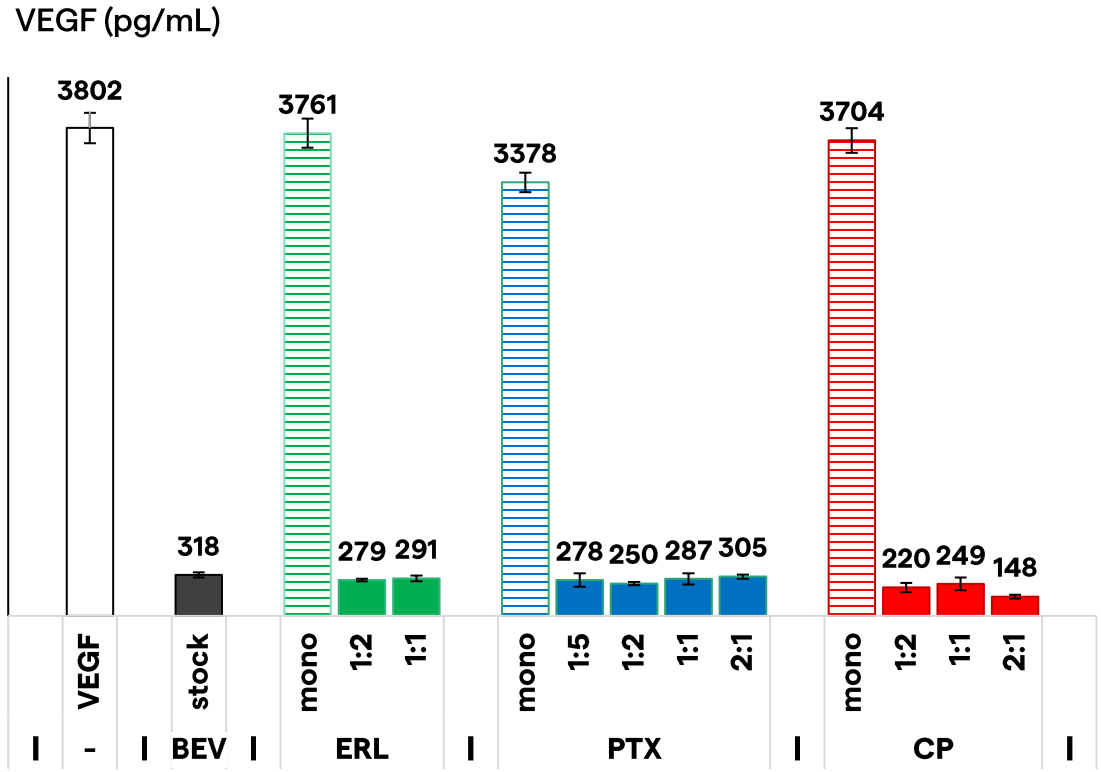
ELISA-based VEGF activity assay



Confirmed bevacizumab survives the simul-spray process with anti-VEGF activity intact

- Reconstitute powders in buffer
- Incubate beva-containing solution with VEGF
- Quantify remaining unbound VEGF with assay
- Mono therapies (without beva) do not inhibit VEGF on their own

Conclusions for case study 2

Simul-spray for combination products

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Simul-spray drying enables unique combination therapies

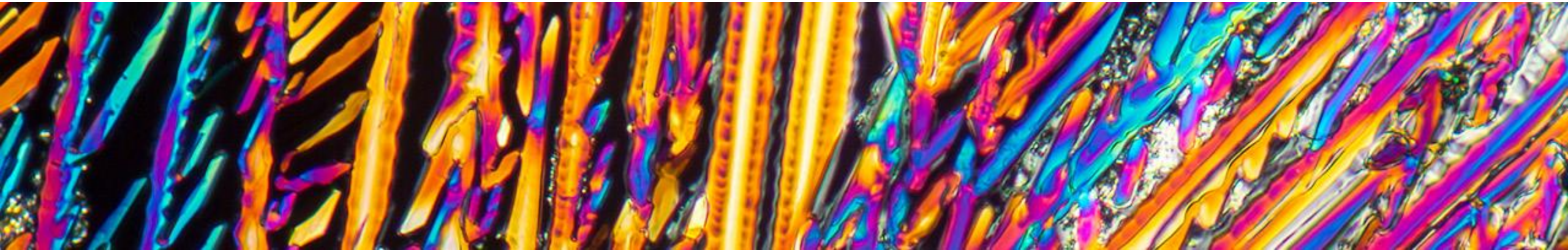
- Simul-spray atomizes two separate liquid feeds into a single spray dryer
- Collected as a uniform blend of two formulations in a single unit operation
- No carriers needed; compatible with low and high dose actives

Cancer-relevant beva/ small molecule formulations

- Manufactured inhalation combination dry powders of beva with erlotinib, paclitaxel and cisplatin
- Formulations achieved target drug concentration, good aerosol properties and preserved anti-VEGF bioactivity

Simul-spray for dose escalation with placebo

- One active stream and one placebo stream used to vary active concentration without changing individual formulations
- May help with dose escalation studies where delivered dose is fill-dependent



Thank you!

Q&A