Aerosol therapy of mAbs

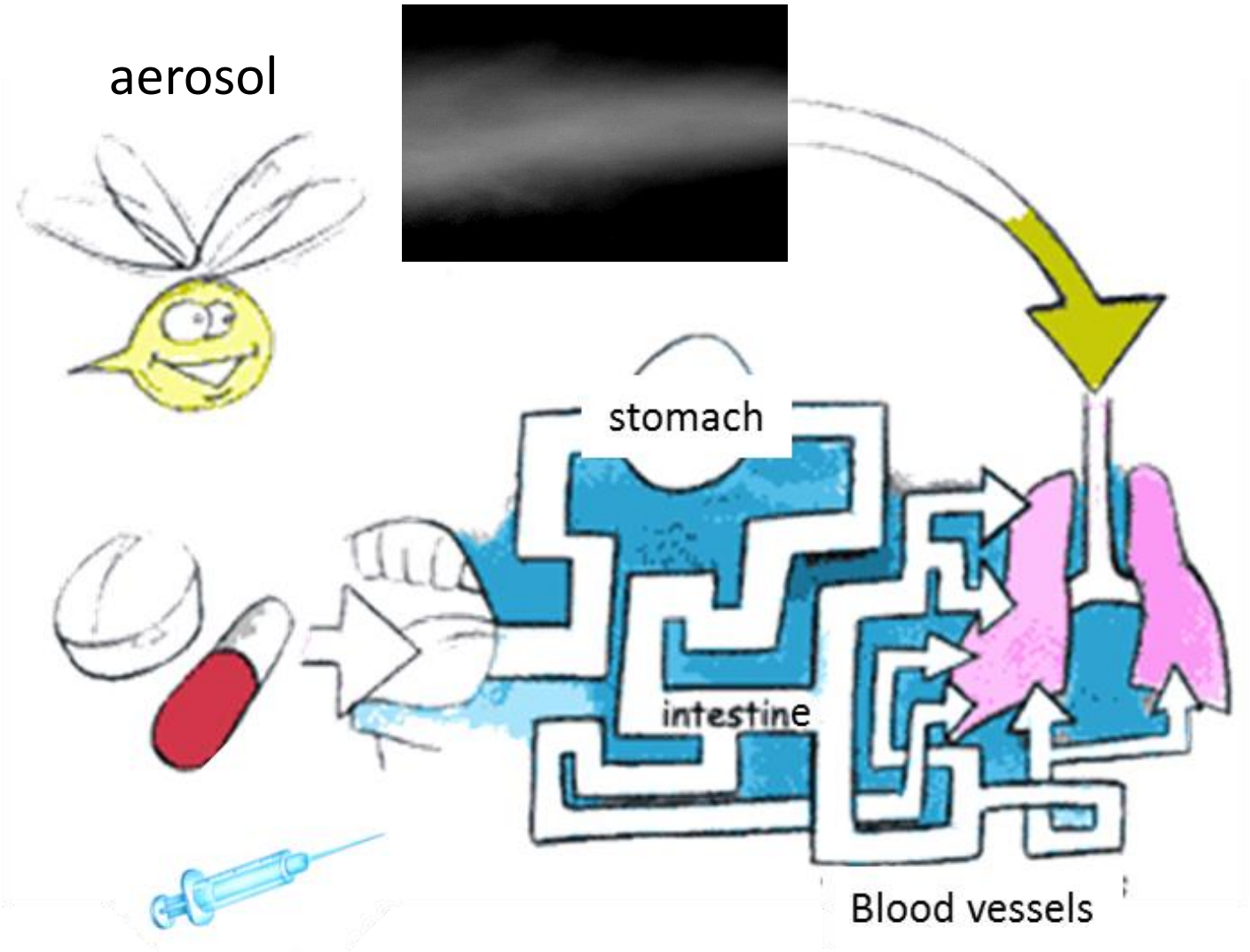
administration by aerosol

Nathalie Heuzé-Vourc'h

Financial supports:

CEPR Inserm U1100 Centre d'Etude des Pathologies Respiratoires

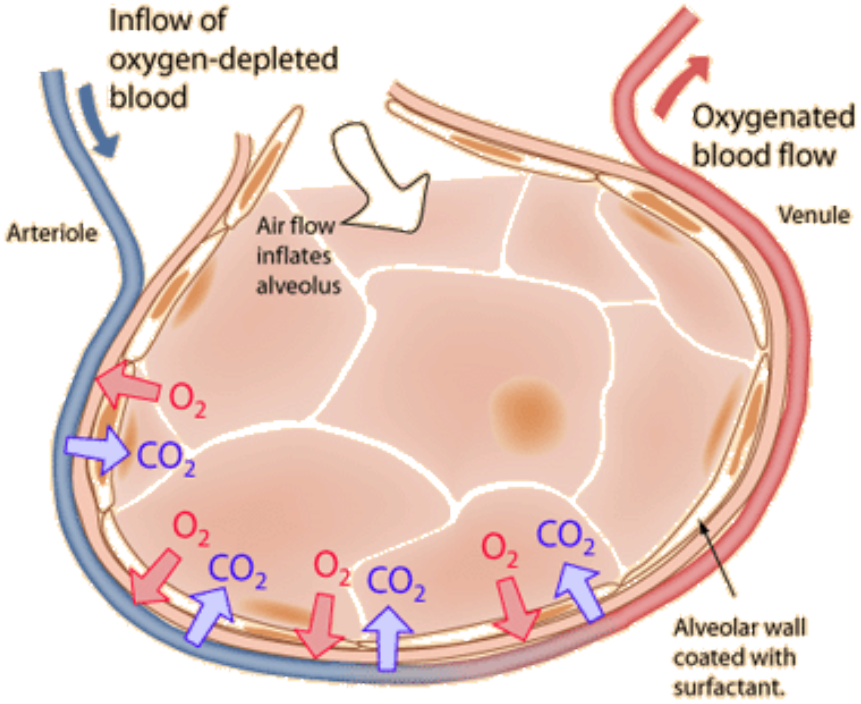
Aerosol therapy



Aerosol therapy for drugs with systemic action

- Airways as a portal for systemic effects

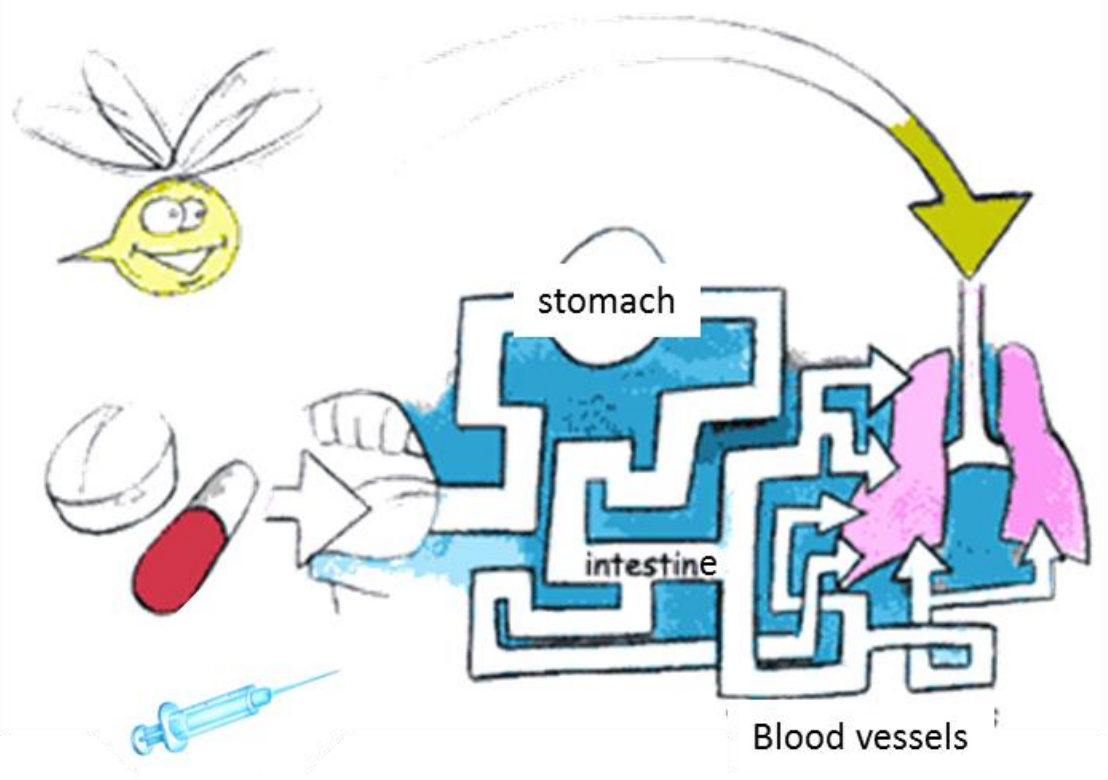
Air-blood barrier = 75 m^2



small molecules: fentanyl, apomorphine hydrochloride

biologics: insulin *(Afrezza®, MannKind Corporation)*

Aerosol therapy of drugs with local action
Respiratory diseases



Therapeutic index

Therapeutic effect Safety

small molecules: b2-adrenoreceptor agonists, muscarinic antagonists and corticosteroids

biologics: Dornase alfa (Pulmozyme®, Roche)

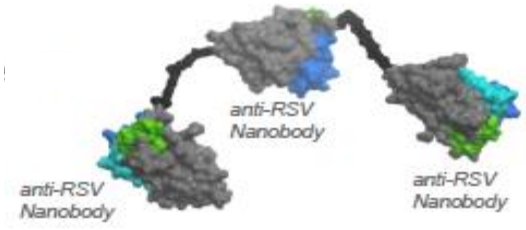
Aerosol therapy of Antibody-based therapeutics in respiratory diseases

- Approved or in Phase III clinical studies

Sponsoring company	INN or code name	Molecular format	Target(s)	Current Phase	Phase III indications
Genentech/Roche - Novartis	Omalizumab	Humanized IgG1	IgE	Approved	Asthma
MedImmune	Palivizumab	Humanized IgG1	RSV	Approved	Prevention of RSV infection
Genentech/Roche	Bevacizumab	Humanized IgG1	VEGF	Approved	NSCLC
GlaxoSmithKline	Mepolizumab	Humanized IgG1	IL-5	Phase III	Asthma; hypereosinophilic syndrome; chronic obstructive pulmonary disease with eosinophilic bronchitis
Teva	Reslizumab	Humanized IgG4	IL-5	Phase III	Eosinophilic asthma
AstraZeneca	Benralizumab	Humanized IgG1	IL-5R	Phase III	Asthma
Hoffmann-La Roche	Lebrikizumab	Humanized IgG4	IL-13	Phase III	Severe asthma
Peregrine	Bavituximab	Chimeric IgG1	Phosphatidylserine	Phase III	NSCLC
Genentech/Roche	MPDL3280A	Human IgG1; Fc engineered	Programmed death-ligand 1	Phase III	NSCLC

Respaud et al. 2015

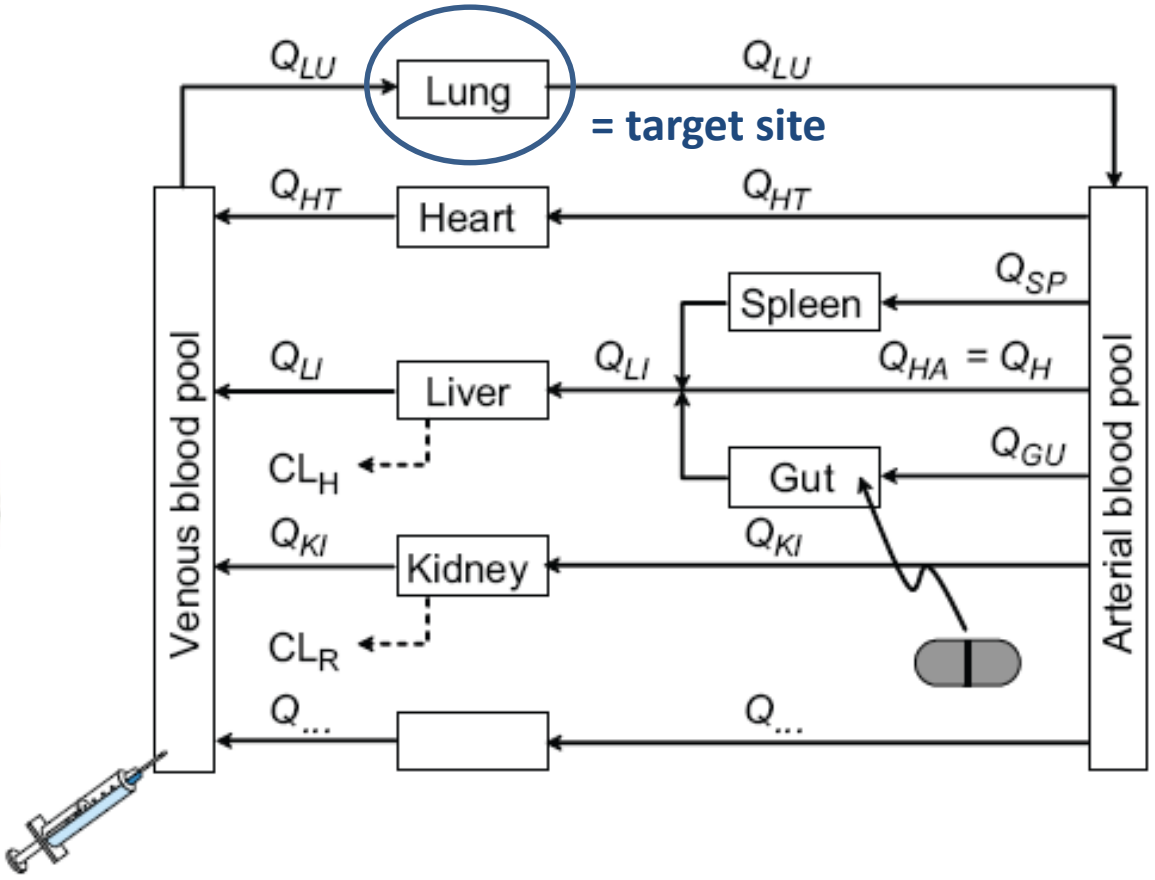
- Inhalation ? ALX-0171 (Ablynx, anti-RSV nanobody™)



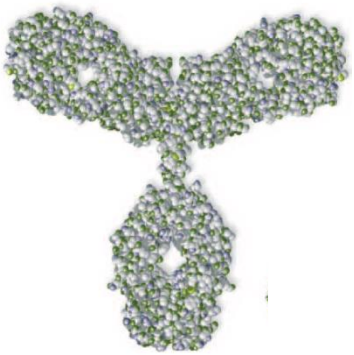
ALX-0171

Rationale to deliver antibody-based therapeutics through the airways

500-10,000 less than in the bloodstream



150 KDa protein

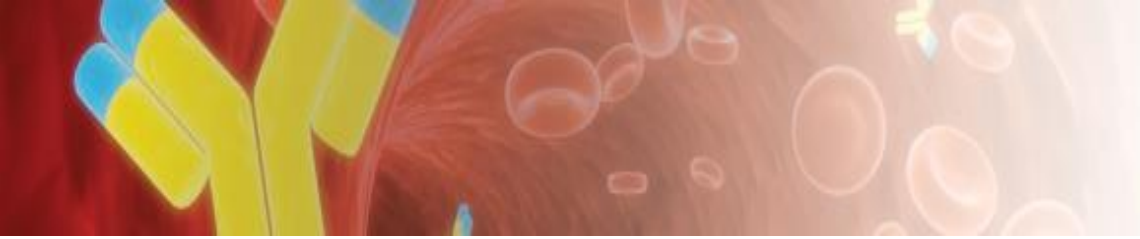


i.v.

s.c. (adalimumab, omalizumab)

i.m. (palivizumab)

Espié P et al. 2009



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Inserm

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is mAb delivery through the airways feasible and relevant for respiratory disease treatment ?

Therapeutic efficacy of mAbs delivered through the airways

A549 Luc – human NSCLC

cetuximab
anti-EGFR (human)
(Merck)

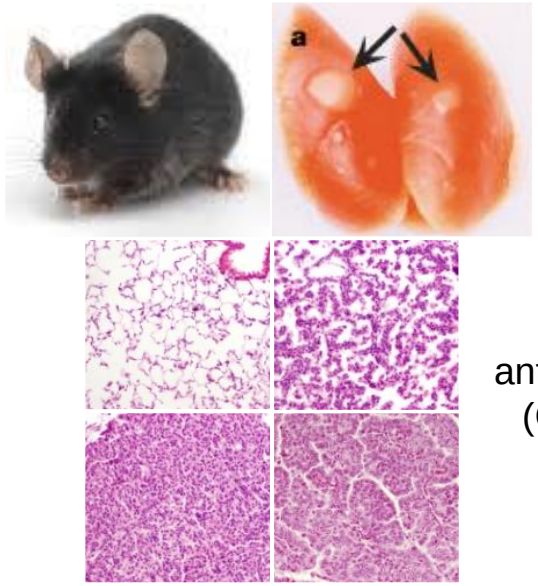
Strength

- ✓ one lesion, alveolar diffusion
- ✓ bioluminescence imaging

Weakness

- ✓ immunodeficient animal
- ✓ do not cross-react with murine EGFR

Kras LA1 model



Murine IgG2a
anti-VEGF mice/human
(G6-31, Genentech)

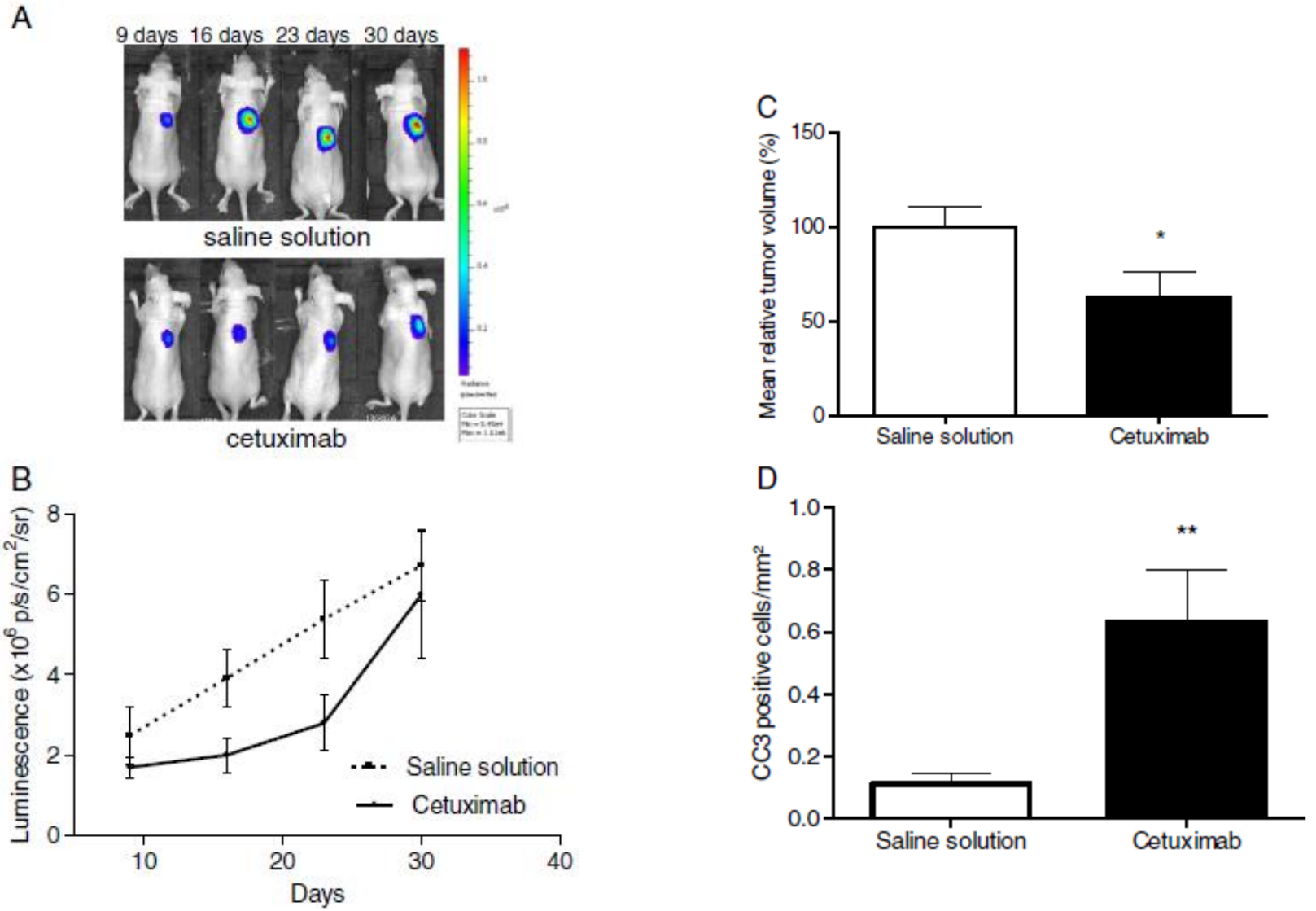
Strength

- ✓ lepidic NSCLC (natural history)
- ✓ normal immune system

Weakness

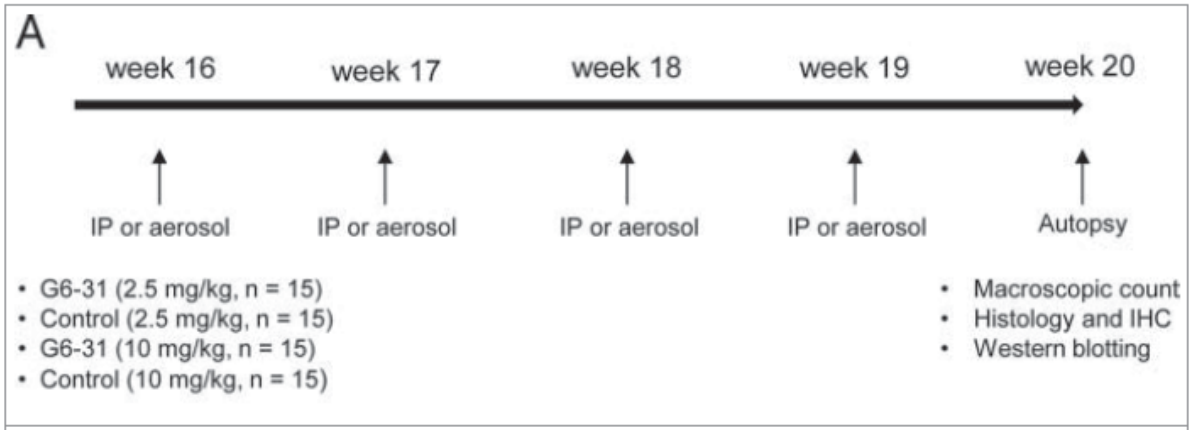
- ✓ mutliple foci

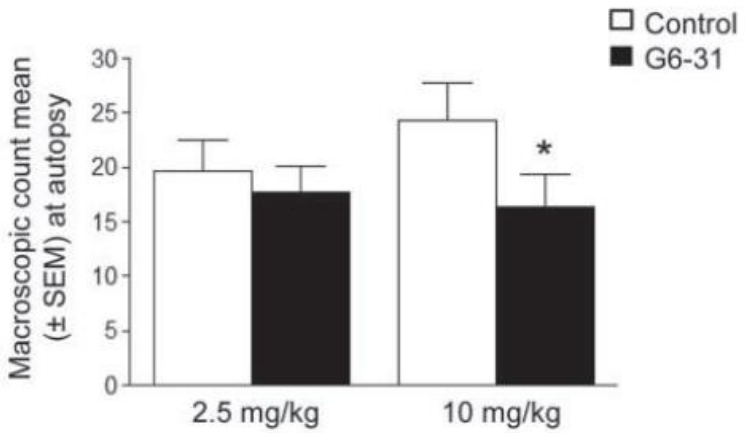
Cetuximab, anti-EGFR in A549-Luc nude mice



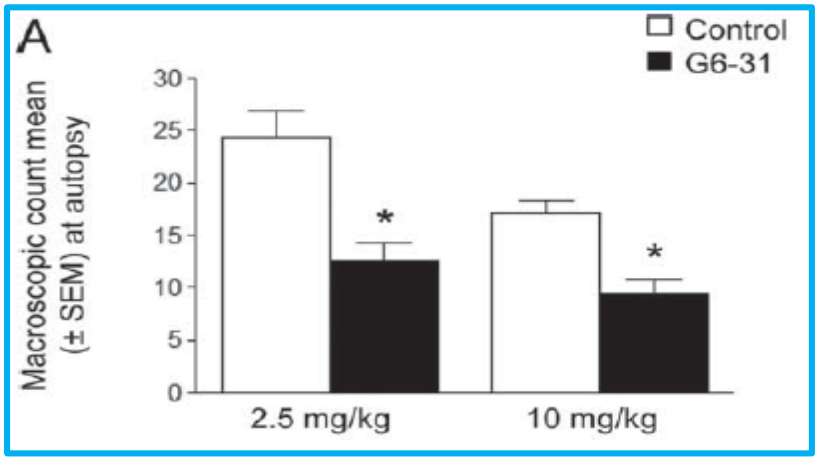
Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014

anti-VEGF in Kras LA1 mice





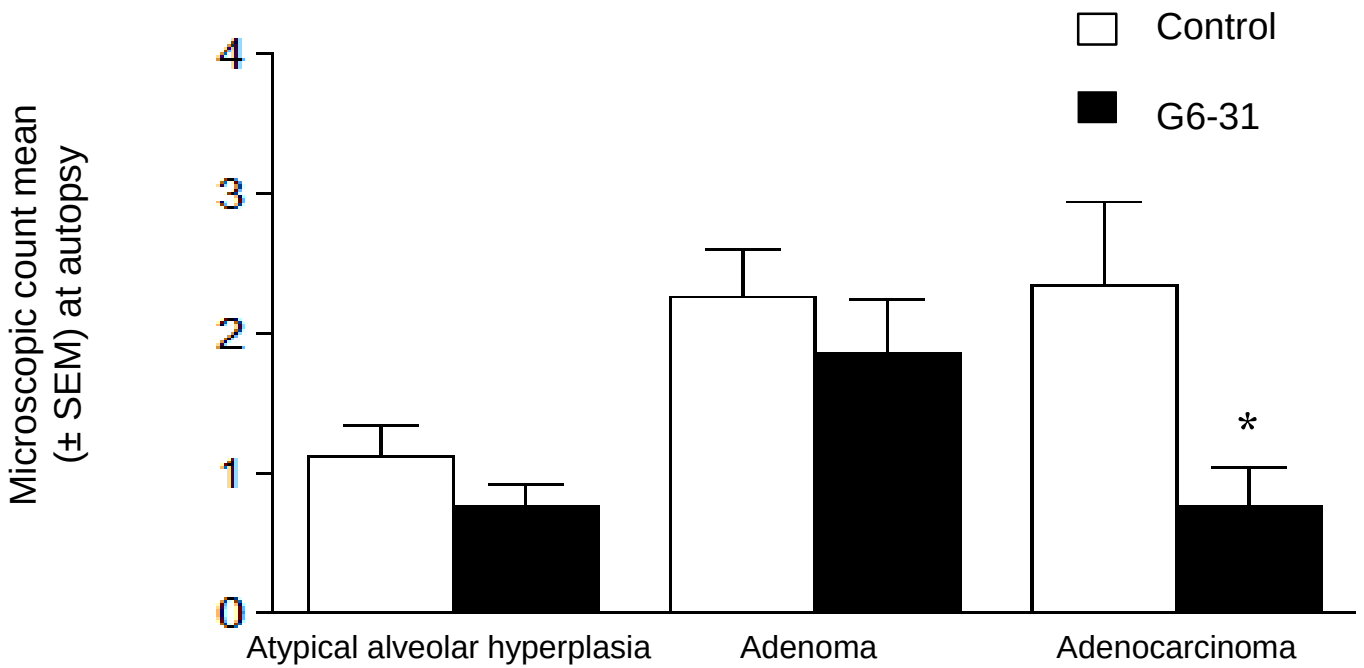
i.p. (systemic)

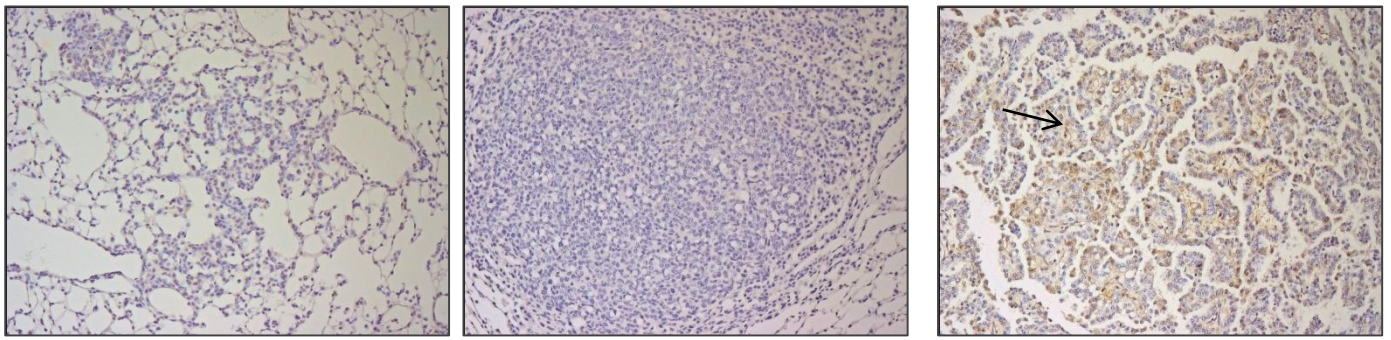


airways

VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014

anti-VEGF in Kras LA1 mice

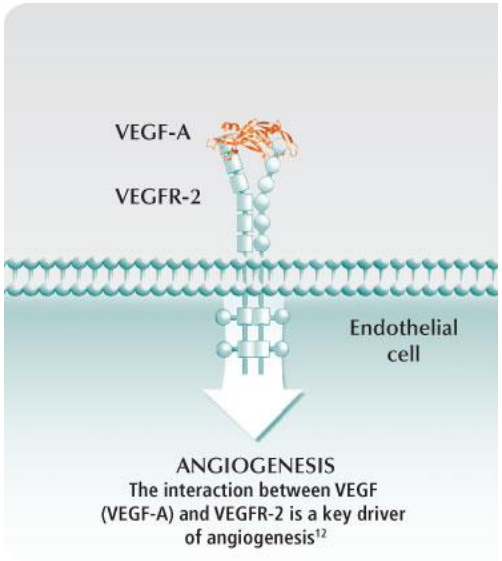




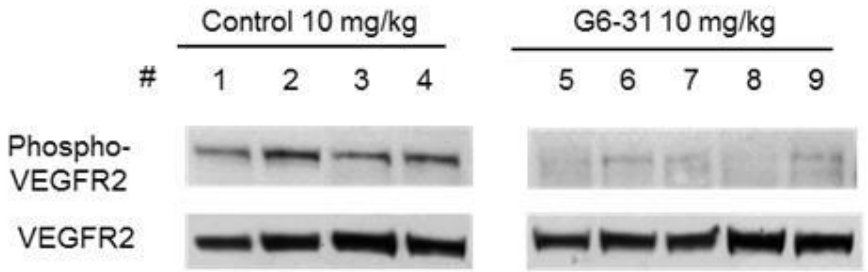
VEGF IHC in Kras LA1 model during tumorigenesis

VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014

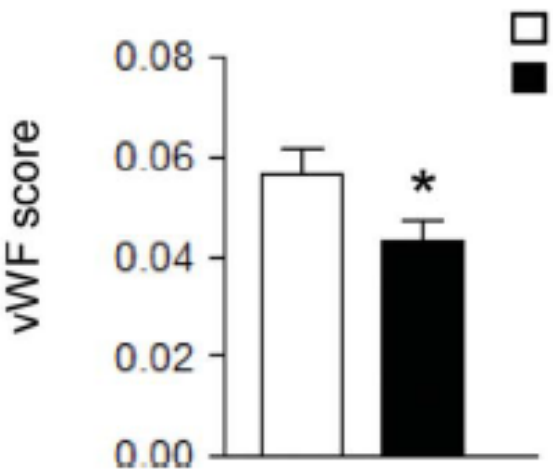
Anti-VEGF in Kras LA1 model
anti-VEGF limited tumor angiogenesis

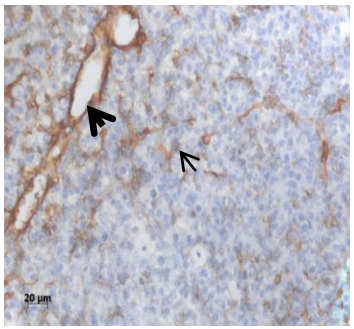


Inhibition of VEGFR2 pathway:



Microvascular density:



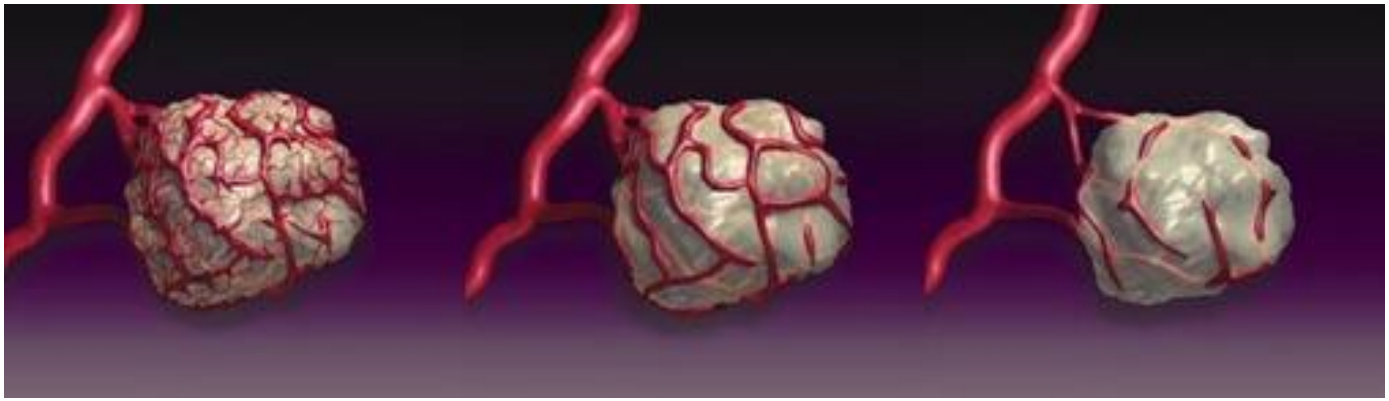


vWF % (± SEM)

	IP	Aerosol
Small vessel (<10 µm)	+ 9.85 (± 20.05) *p* = 0.96	**- 44.21** (± 7.67) *p* = 0.018
Large vessel (>10 µm)	**- 43.10** (± 12.09) *p* = 0.0096	- 11.50 (± 14.69) *p* = 0.27

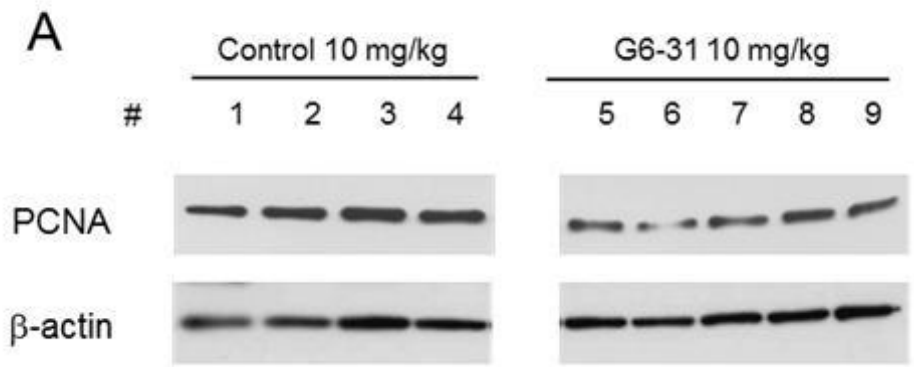
VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014

Anti-VEGF in Kras LA1 model anti-VEGF limited tumor growth



genentech, Inc.

Proliferative index:



VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014

Biodistribution of mAbs delivered through the airways

A549 Luc – human NSCLC

cetuximab
anti-EGFR (human)
(Merck)

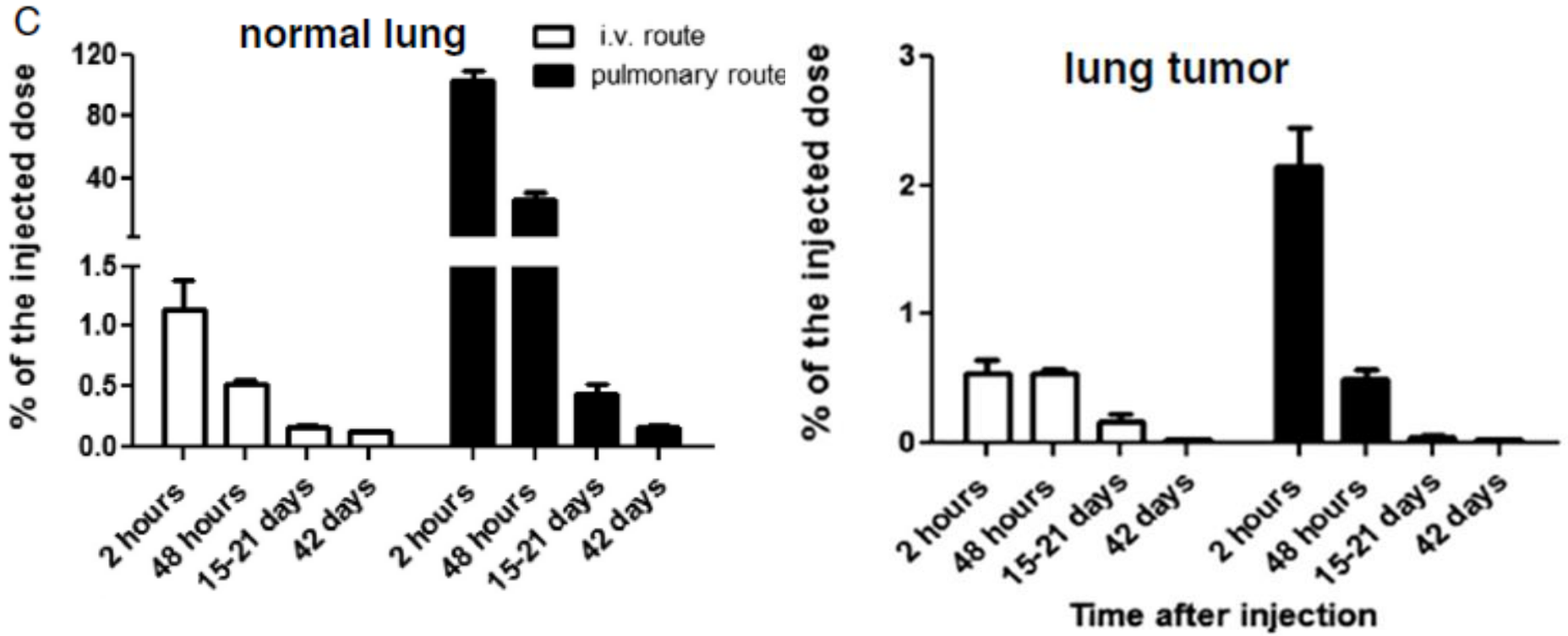
NIRF imaging

✓ cetuximab conjugated to a fluorophore

IHC for cellular localization

✓ anti-human IgG

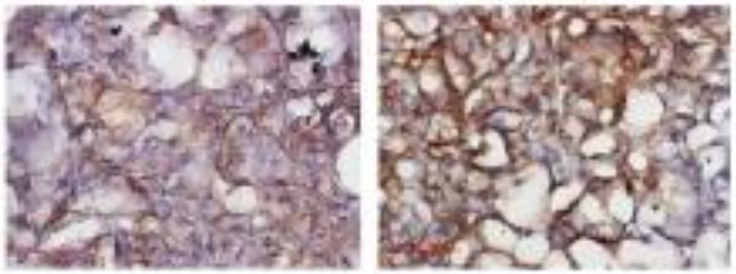
Biodistribution of mAbs delivered through the airways



Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014

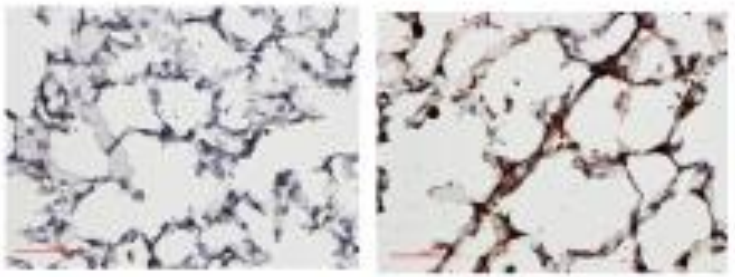
Biodistribution of mAbs delivered through the airways

i.v. route pulmonary route



Lung tumor

Bronchial epithelium + tumor



Alveolar epithelium

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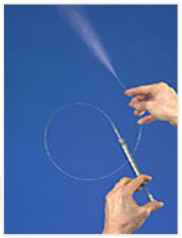
Pharmacokinetics of mAbs delivered through the airways

mAbs (only full-length)

- ✓ anti-VEGF (G6-31, Genentech)
- ✓ Anti-EGFR (cetuximab, Merck)
- ✓ Anti-CD20 ….

Animals

- ✓ WT animals

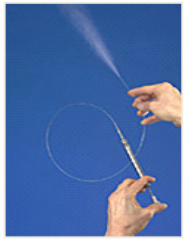
Healthy/tumor model

mAbs (only full-length)

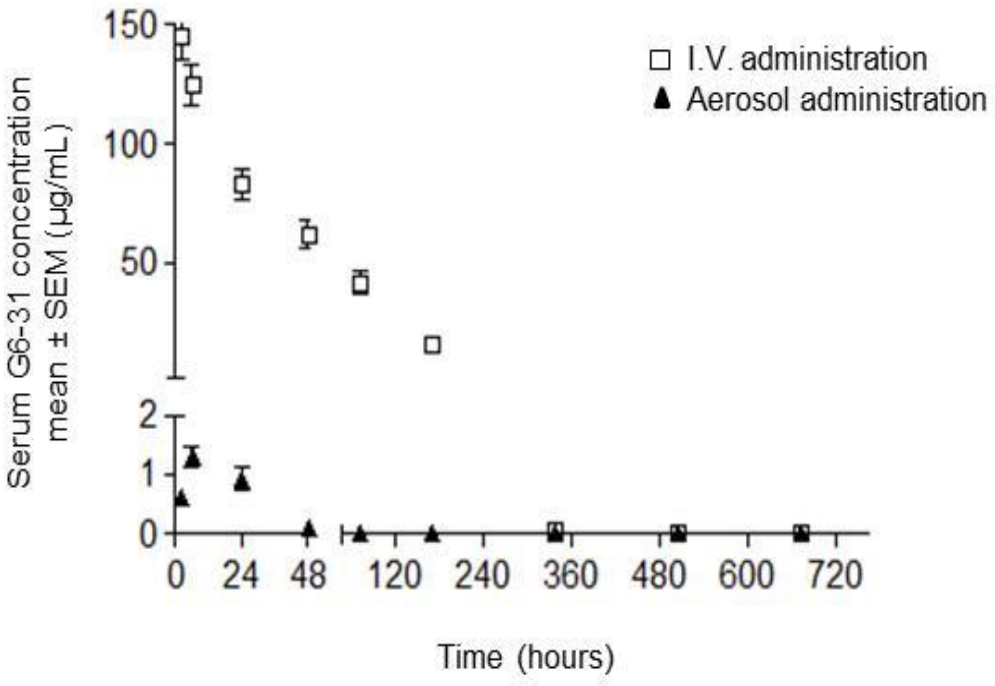
- ✓ Anti-EGFR (cetuximab, Merck)
- ✓Anti-ricin (43RCA, French Army)

Devices

- ✓ Microsprayer™ (PennCentury)
- ✓ Mesh nebulizer (Aerogen)




Pharmacokinetics of mAbs delivered through the airways



Serum bioavailibility (F)

G6-31 (Kras LA1 mice) 5.1%
cetuximab (normal mice) 3.9%
rituximab (normal mice) 6.2 %

cetuximab (NHP) 0.3%
Anti-ricin (NHP) <1%

Mean residence time (MRT)

cetuximab (normal mice) 12.4 days
rituximab (normal mice) 14.2 days

cetuximab (NHP) 10.9 days

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014

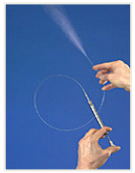
Pharmacokinetics of mAbs delivered through the airways

- Role of FcRn in the passage from the airways into the bloodstream

BL6 WT

Blood sampling

PK analysis



cetuximab or rituximab
one administration, 10mg/kg
i.v. or aerosol

BL6 KO FcRn

PK analysis

Blood sampling

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014

Pharmacokinetics of mAbs delivered through the airways

Table 2

Estimated non-compartmental pharmacokinetic parameters for cetuximab in WT and FcRn KO mice. AUC: area under the concentration–time curve; AUMC: area under the first-moment concentration–time curve; MRT: mean residence time; $t_{1/2}$: half-life for elimination; MAT: mean absorption time; F: bioavailable fraction.

	CETUXIMAB	
	FcRn WT	FcRn KO
I.v. route	n = 8	n = 7
$AUC_{0\rightarrow\infty}$ ($mg \cdot L^{-1} \cdot day$)	942.9	39.0
$AUMC_{0\rightarrow\infty}$ ($mg \cdot L^{-1} \cdot day^2$)	9851.4	19.4
MRT (day)	10.4	0.5
$t_{½}$ (day)	7.2	0.3
Pulmonary route	n = 9	n = 9
$AUC_{0\rightarrow\infty}$ ($mg \cdot L^{-1} \cdot day$)	37.0	3.1
$AUMC_{0\rightarrow\infty}$ ($mg \cdot L^{-1} \cdot day^2$)	456.8	3.8
MRT (day)	12.4	1.2
$t_{½}$ (day)	8.6	0.9
F	3.9%	7.9%
MAT (day)	1.9	0.7

idem with rituximab

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014

Conclusions

✓ mAb delivery through the airways is “therapeutically” relevant

- Reach their target antigen and pharmacologically effective
- Limited passage into the bloodstream

in pathophysiological conditions ?

not only dependent on FcRn – lymph vessels ?

- Safety/immunogenicty

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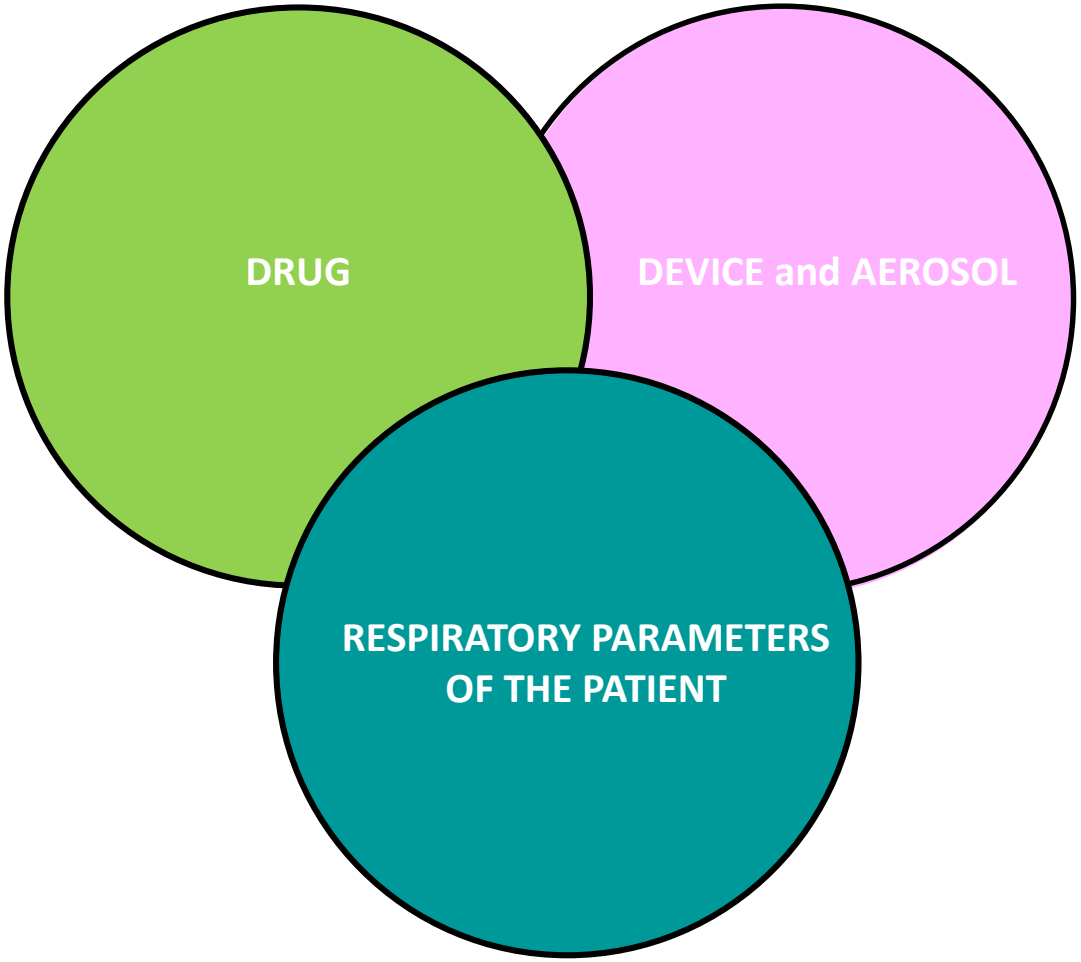
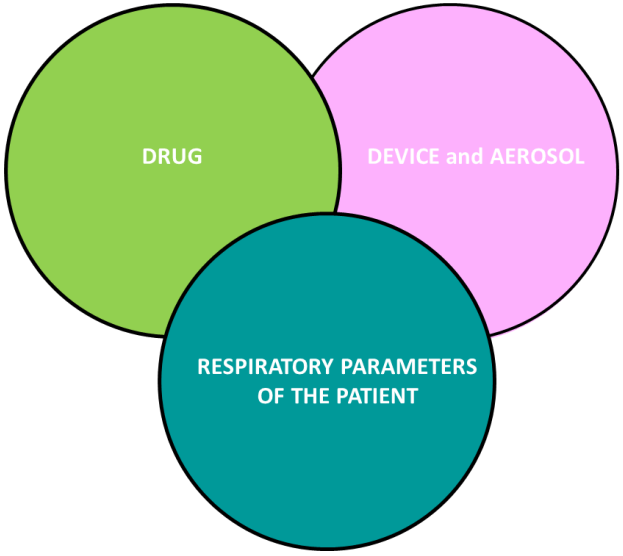
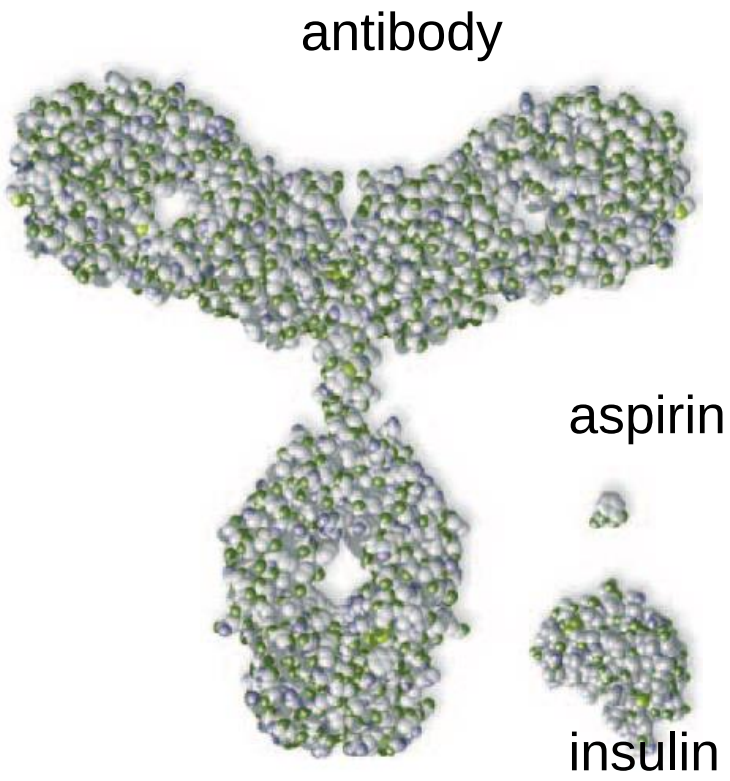
Issues related to Aerosol therapy



Issues related to Aerosol therapy





- Complexed macromolecules (150 KDa)
- Prone to chemical/physical degradation (in particular at the air-liquid interface)

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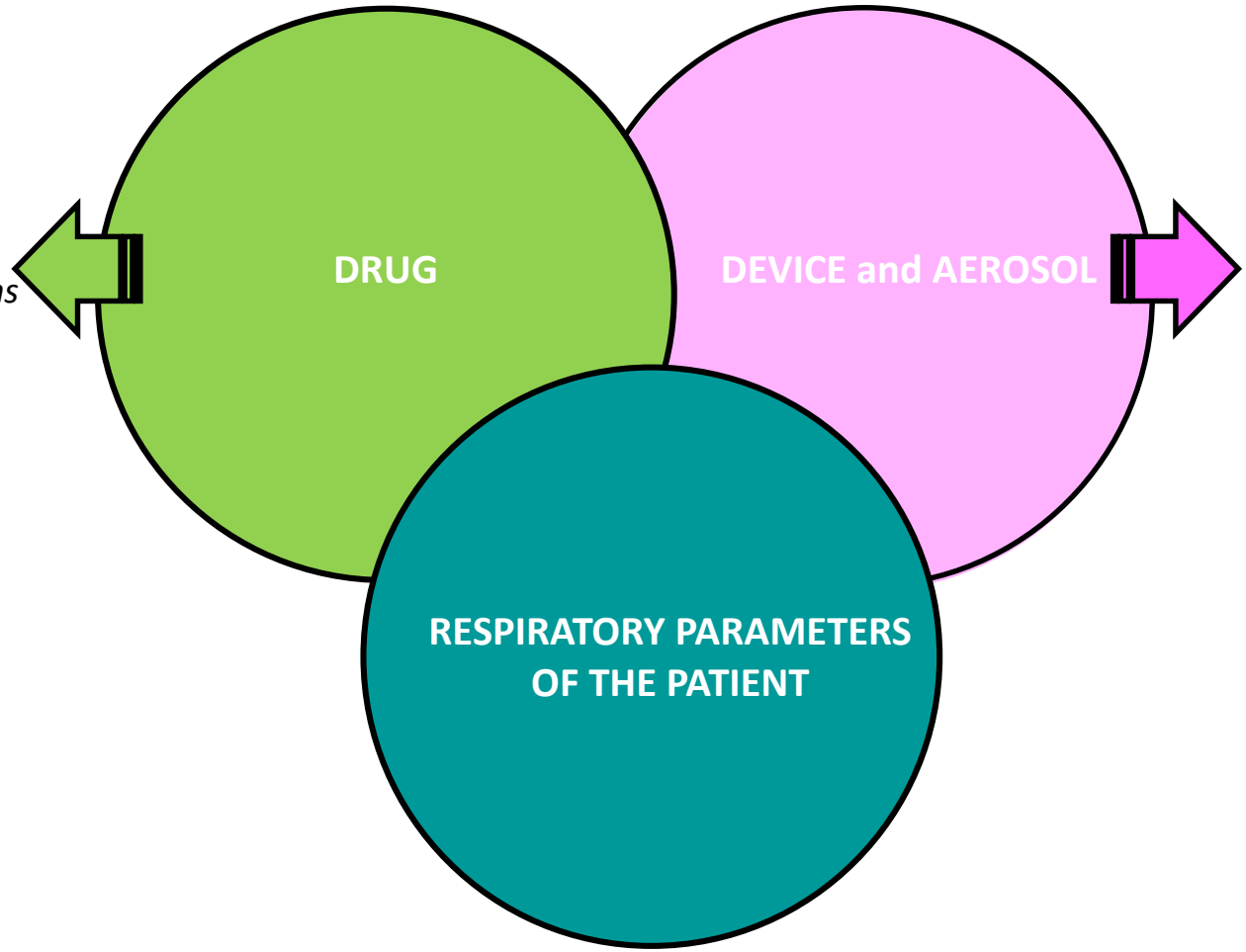
Issues related to Aerosol therapy

Renaud Respaud
Aerosol formulations



Laurent Vecellio
Nebulisation devices

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Jeoffrey Pardessus
Flora Paul
Renaud Respaud
Laurent Vecellio….

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