CLINICAL

Future PIPAC Research

Marc A. Reymond, MD, MBA

Professor of Surgery, University of Tübingen, Germany

Director, National Center for Pleura and Peritoneum

Disclosures

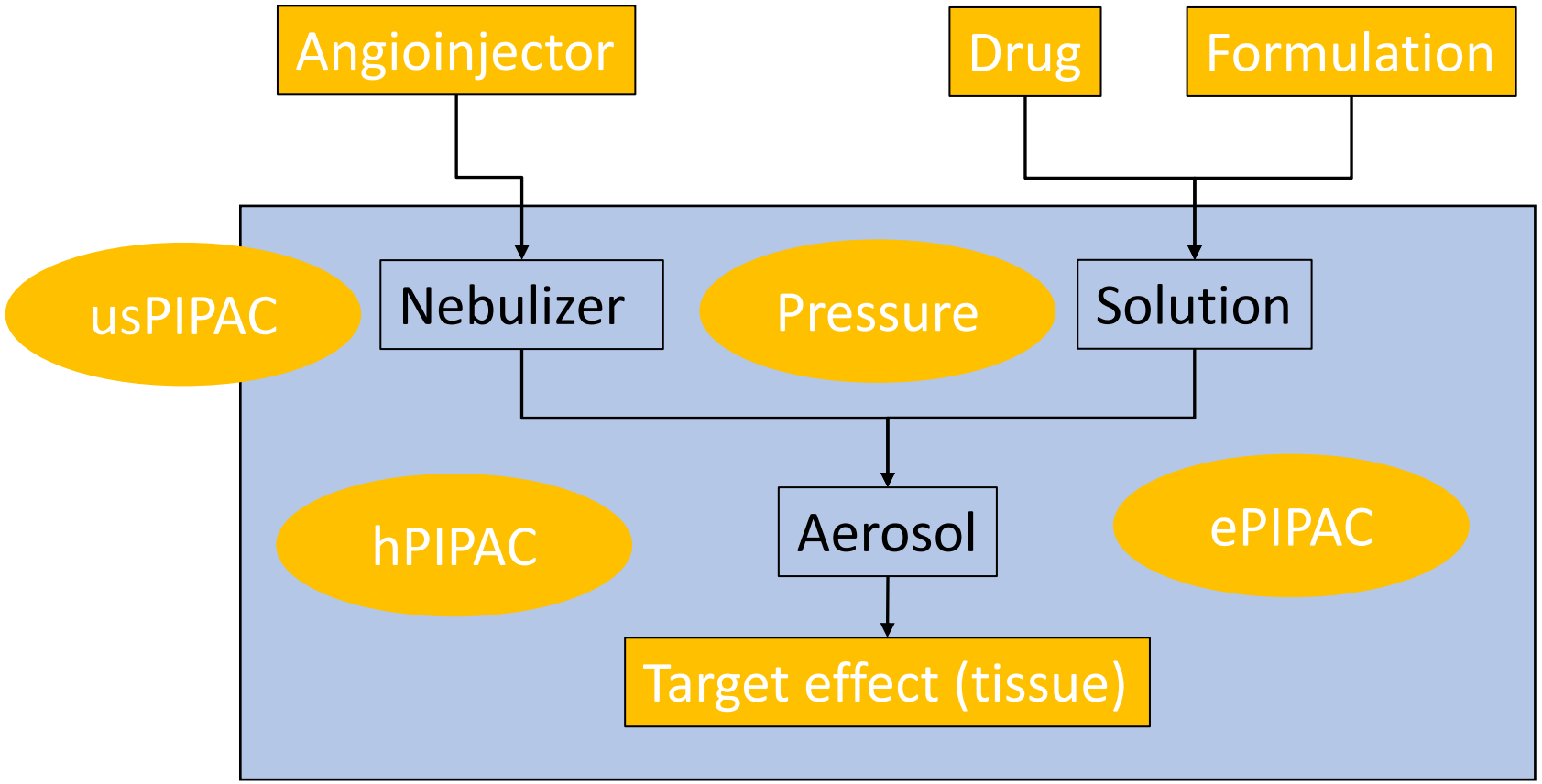
- CEO/Owner of Capnomed GmbH
- CEO/Owner of Capnopharm GmbH

These disclosures have been deemed as irrelevant, as this presentation is limited to basic science research, such as pre-clinical research and drug discovery, or the methodologies of research, and I will not make care recommendations.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

The off-label or investigational use of Cisplatin, Doxorubicin, Oxaliplatin, nab-Paclitaxel will be addressed.

PIPAC: the research space



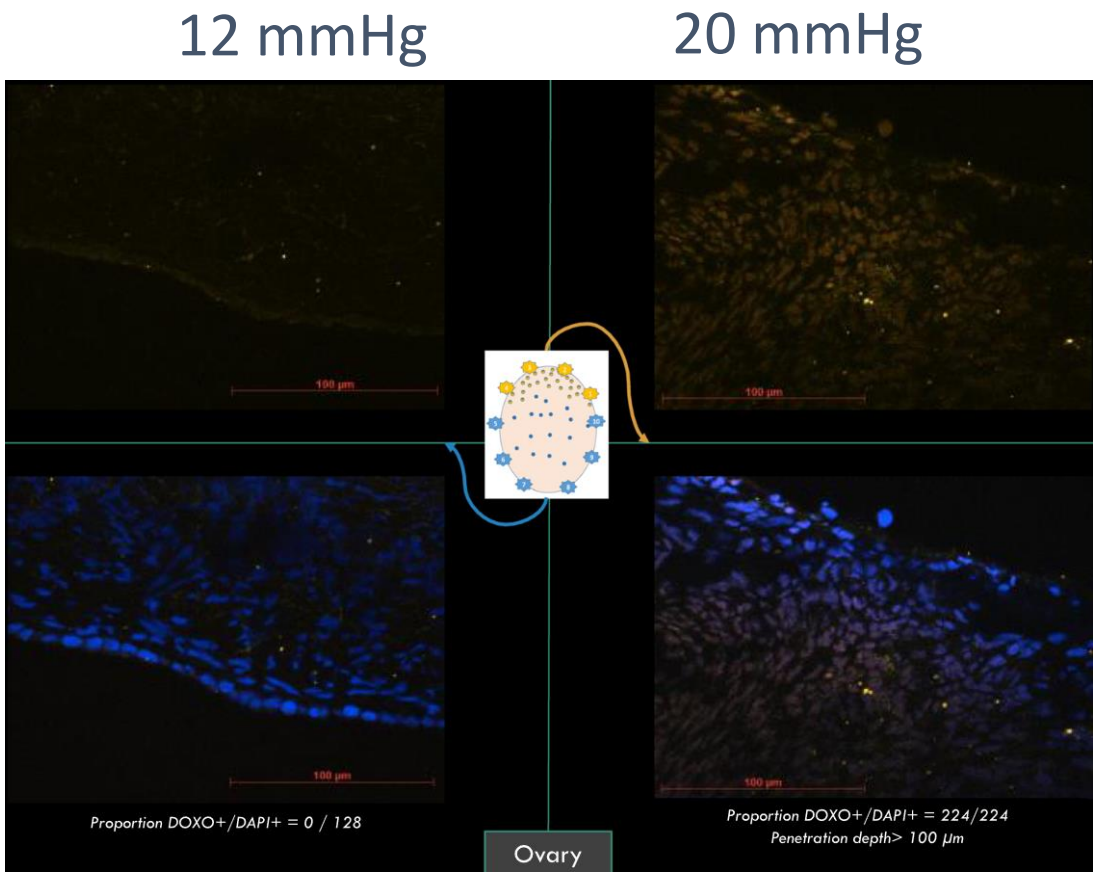
PIPAC is not a therapy but a drug delivery system

The therapeutic effect is achieved by the drug, not the device

Hyperbaric PIPAC (up to 20 mmHg)

1. Significant effect of increased intra-abdominal pressure (20 vs 12 mmHg) on DOX penetration depth
2. Large variations in DOX penetration between abdominal organs
   - omentum > ovary > colon*
3. Large variations between animalsm (sheeps)

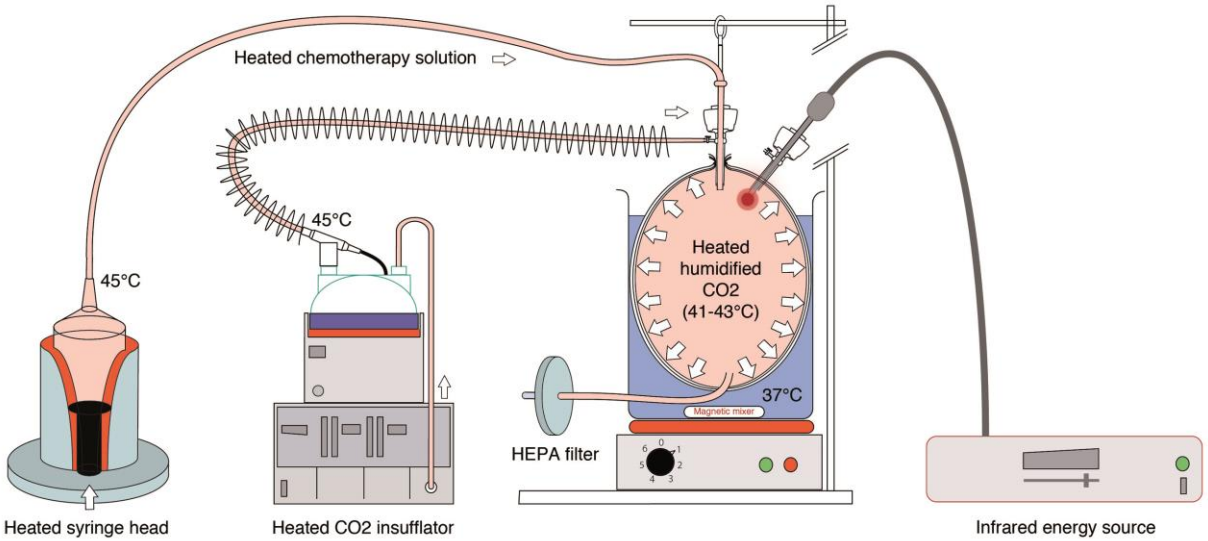
* Explaining HIPEC effect ovarian / colon cancer ?



Green: doxo, Blue: counterstaining (DAPI)

Mimouni et al, BMC cancer 2021

Hyperthermic PIPAC (41-43 °C)

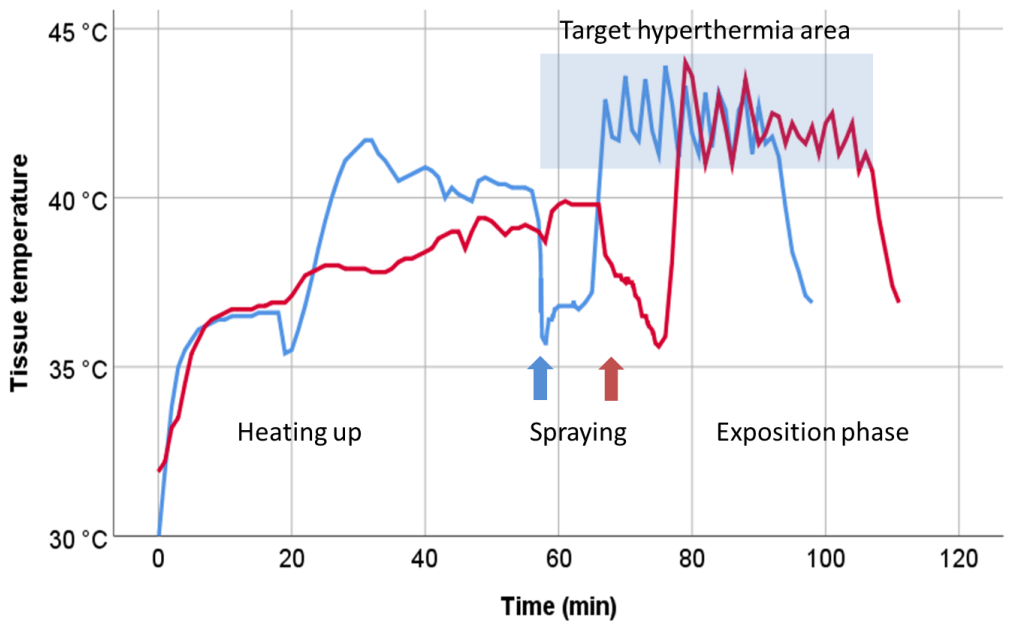


Three heating devices needed

Intraluminal infrared energy delivery

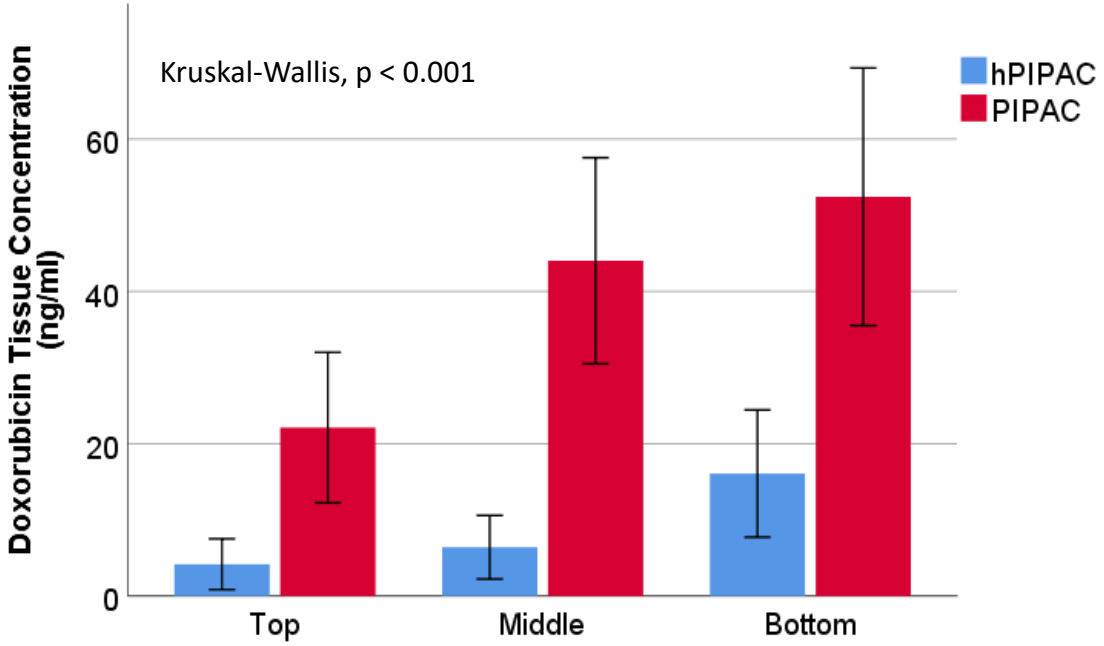
Bachmann C. et al, Surg Endosc 2021

Hyperthermic PIPAC (41-43 °C)



hPIPAC is technically feasible

DOX tisse concentration



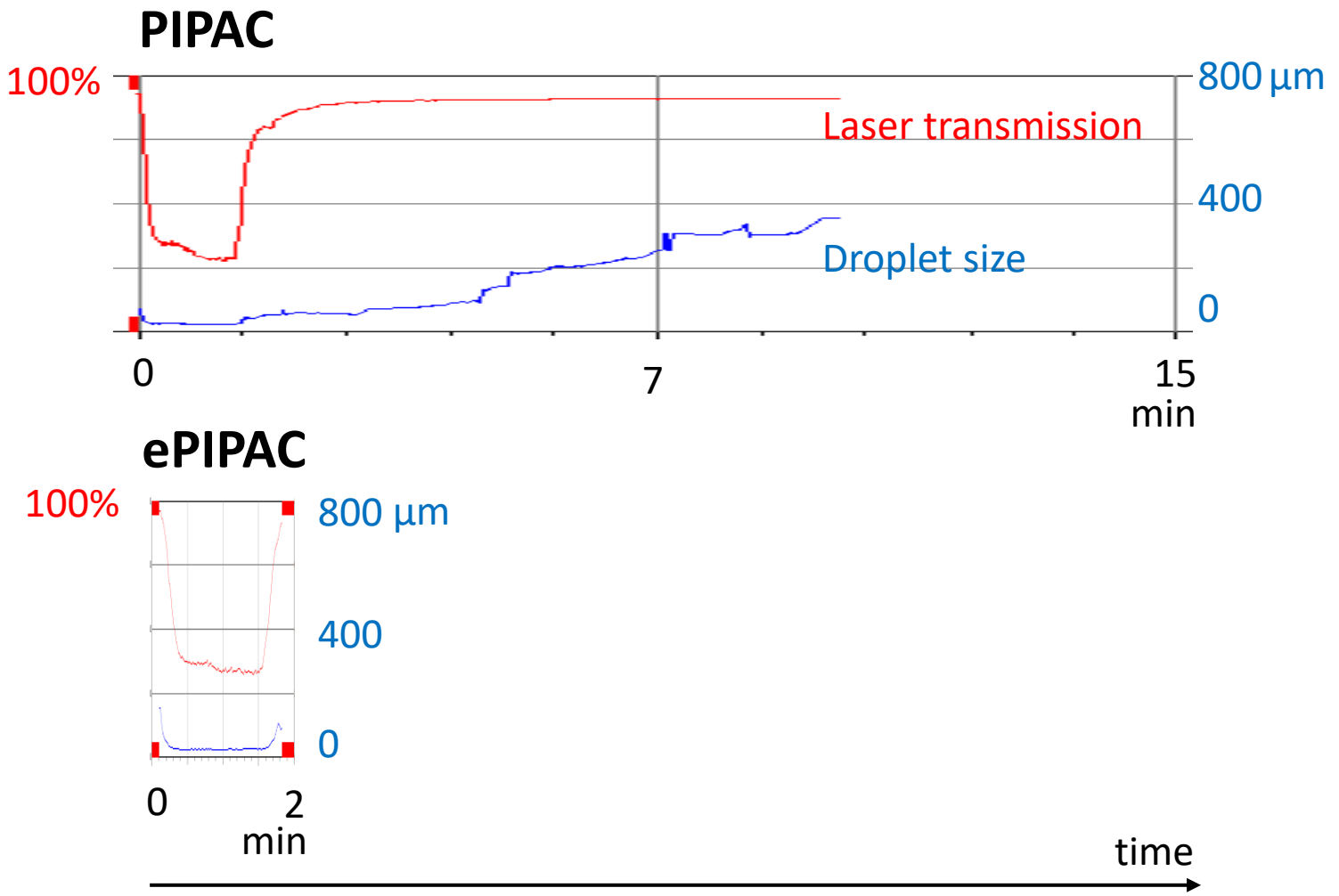
No pharmacological advantage of hPIPAC > PIPAC

Bachmann C. et al, Surg Endosc 2021

Electrostatic loading (ePIPAC): granulometry

1. Aerosol sediments 5 times **faster** after ePIPAC vs PIPAC

2. ePIPAC prevents agglomeration of aerosol particles over time: **smaller Median Aerodynamic Diameter (MAD)**

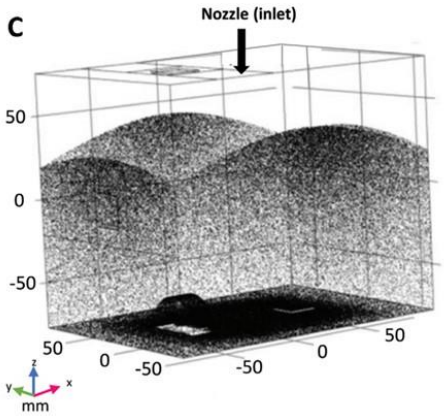


Sautkin I et al, PhD thesis, Tübingen 2022

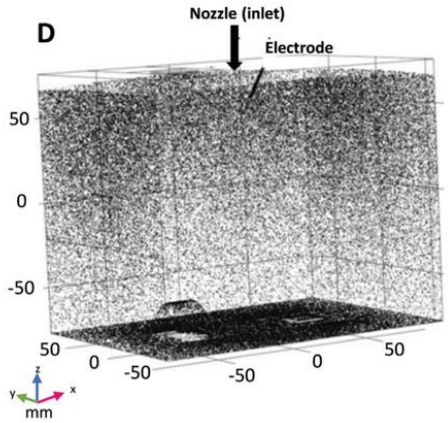
Electrostatic precipitation (e)PIPAC: spatial distribution

Simulation

PIPAC



ePIPAC

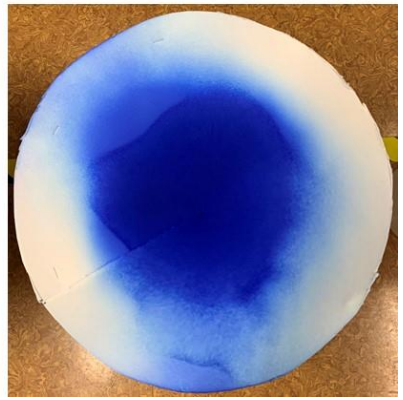


Van de Sande et al, Adv Healthcare Mater 2020

In-vitro experiment

PIPAC

ePIPAC



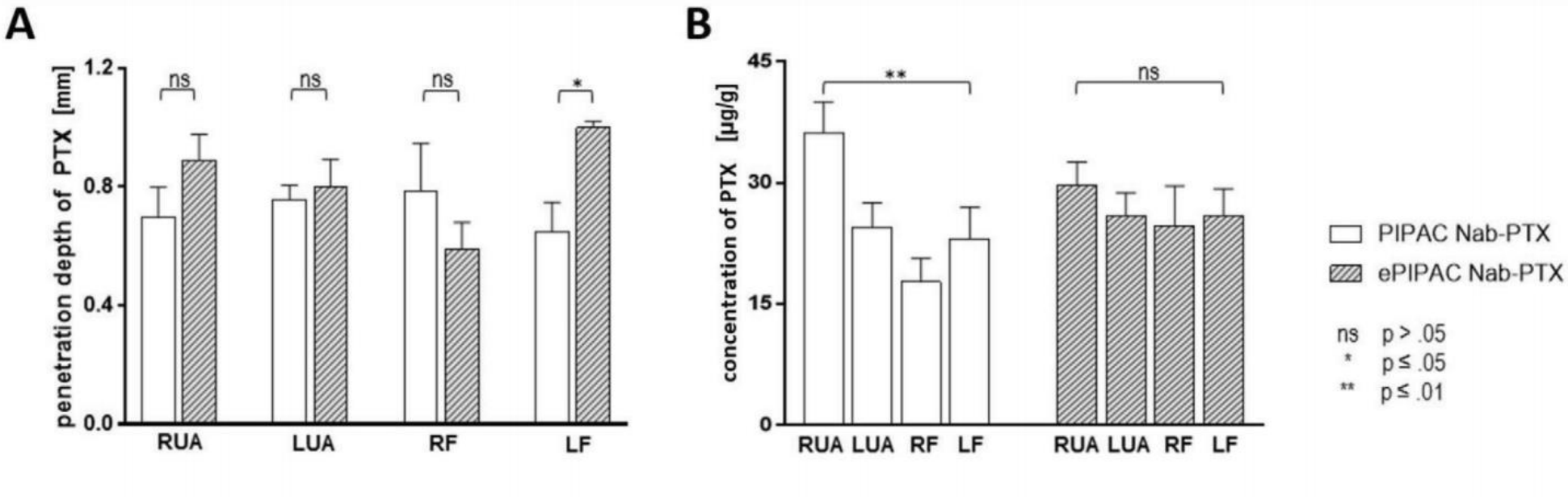
Sautkin I et al, PhD thesis, Tübingen 2022

Spatial distribution **more homogeneous** after ePIPAC vs. PIPAC

ePIPAC: depth of tissue penetration (nab-PTX)

Tissue penetration

Tissue concentration



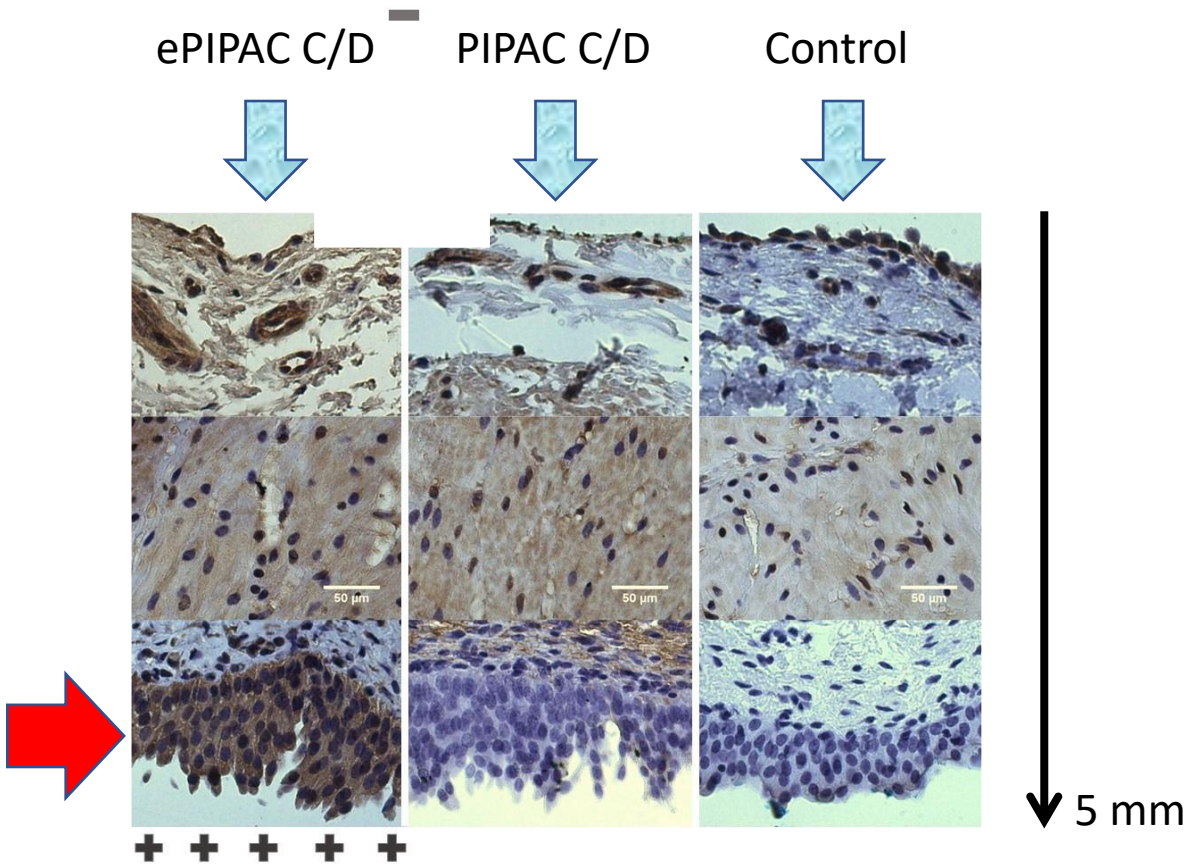
Tissue drug delivery **optimized** after ePIPAC vs. PIPAC

Van de Sande et al, Adv Healthcare Mater 2020

ePIPAC vs. PIPAC : biological effect (DOX)

- Cleaved Caspase-3 (apoptosis marker) as determined by Immunohistochemistry
- Comparison of ePIPAC vs. PIPAC
- eIBUB model

After ePIPAC, apoptosis is observed on the outside bladder surface



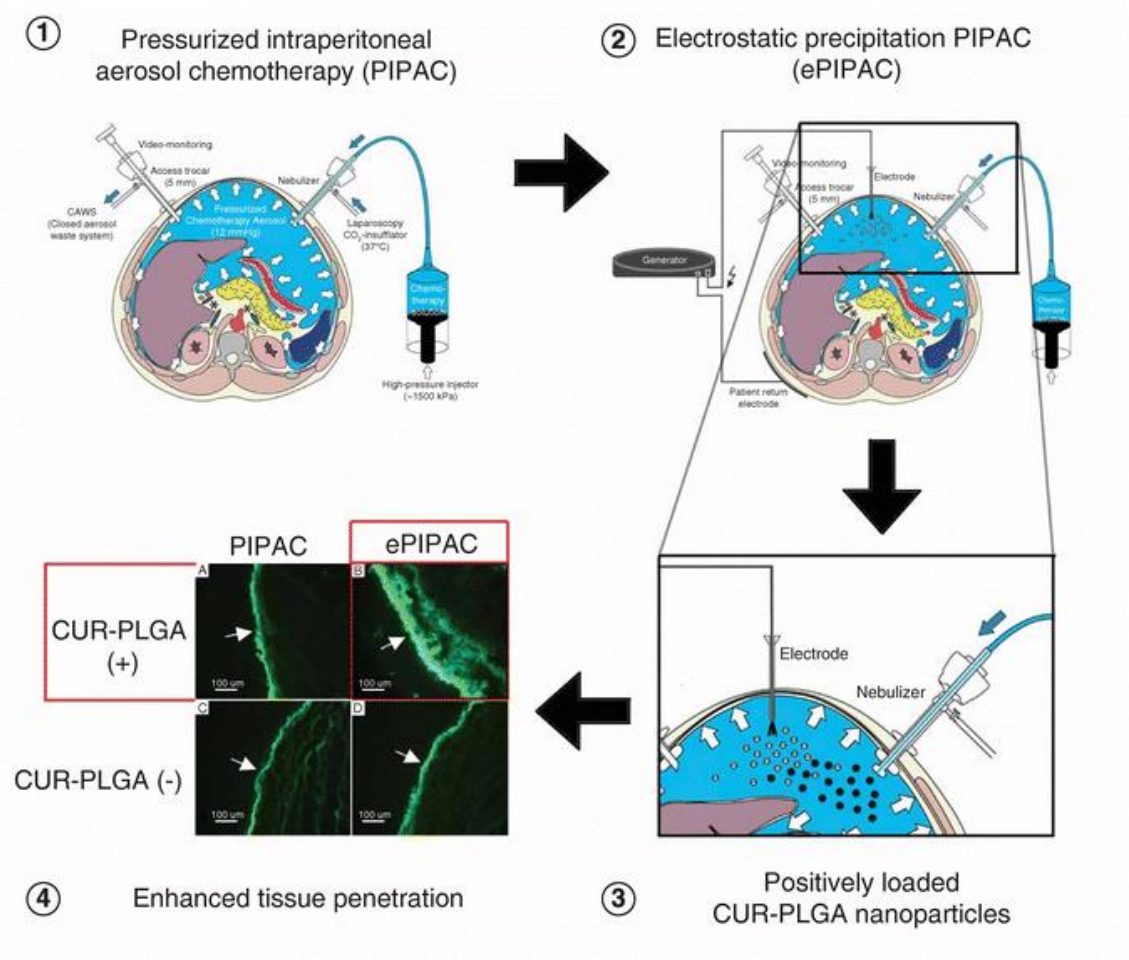
Sautkin I, PhD Thesis

ePIPAC: synergy with charged nanoparticles

Positively charged Curcumin-PLGA nanoparticles
Ex-vivo experiment (inverted bovine urinary bladder, IBUB)

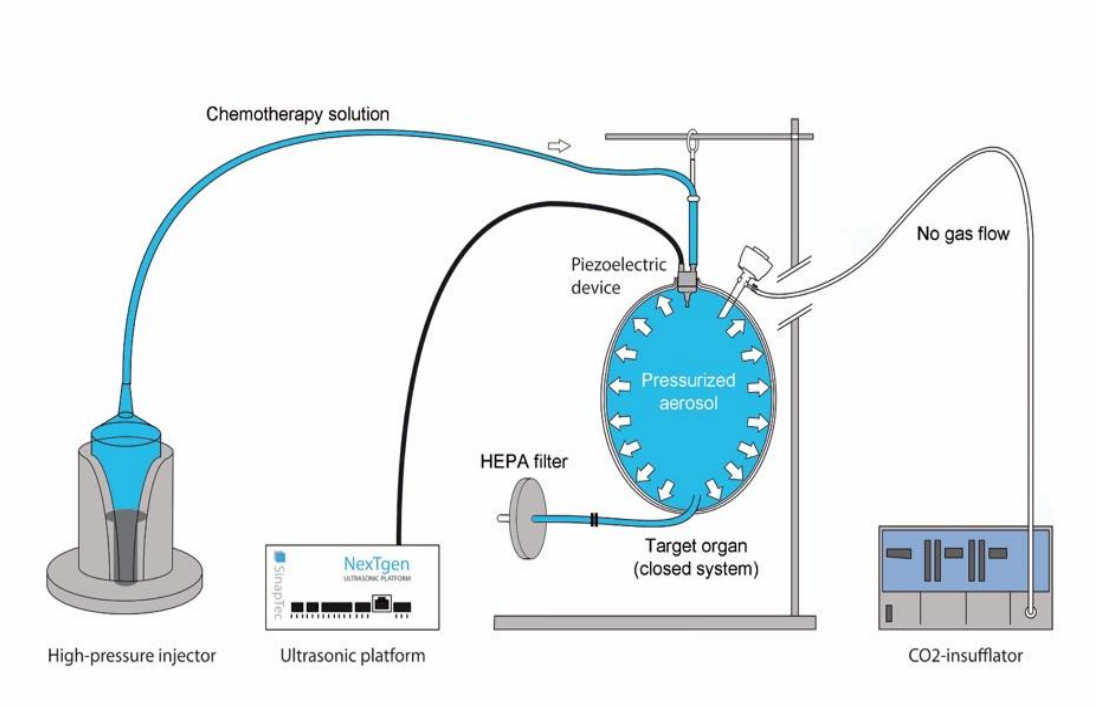
CUR-PLGA-NPs increased:
- depth of tissue penetration by 81.5%
- tissue concentration by 80%.

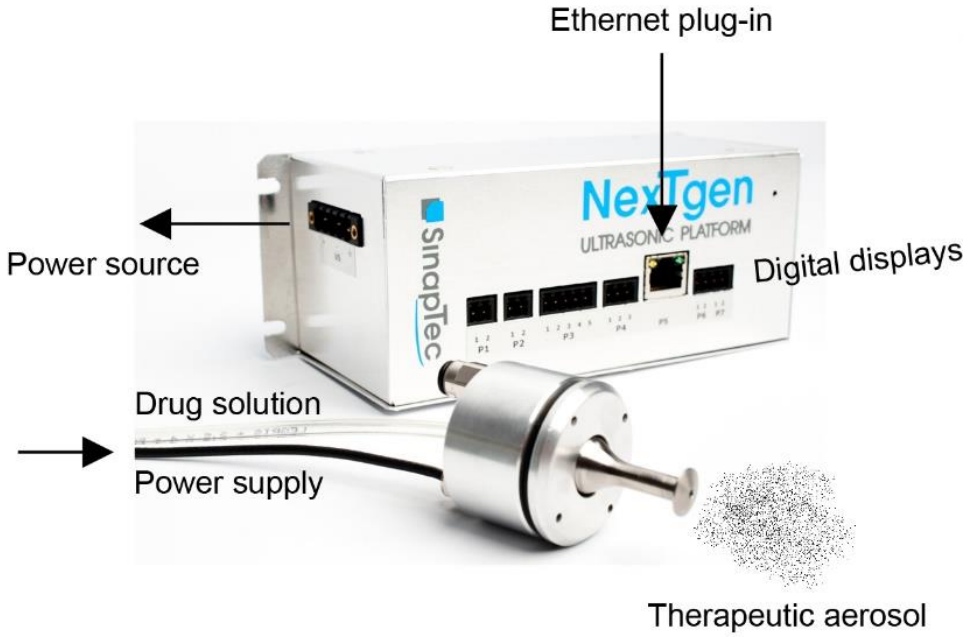
Electrostatic precipitation further improved uptake of positively charged CUR-PLGA-NPs by 41.8%



Castagna A et al, Nanomedicine 2021

Ultrasound PIPAC (usPIPAC)



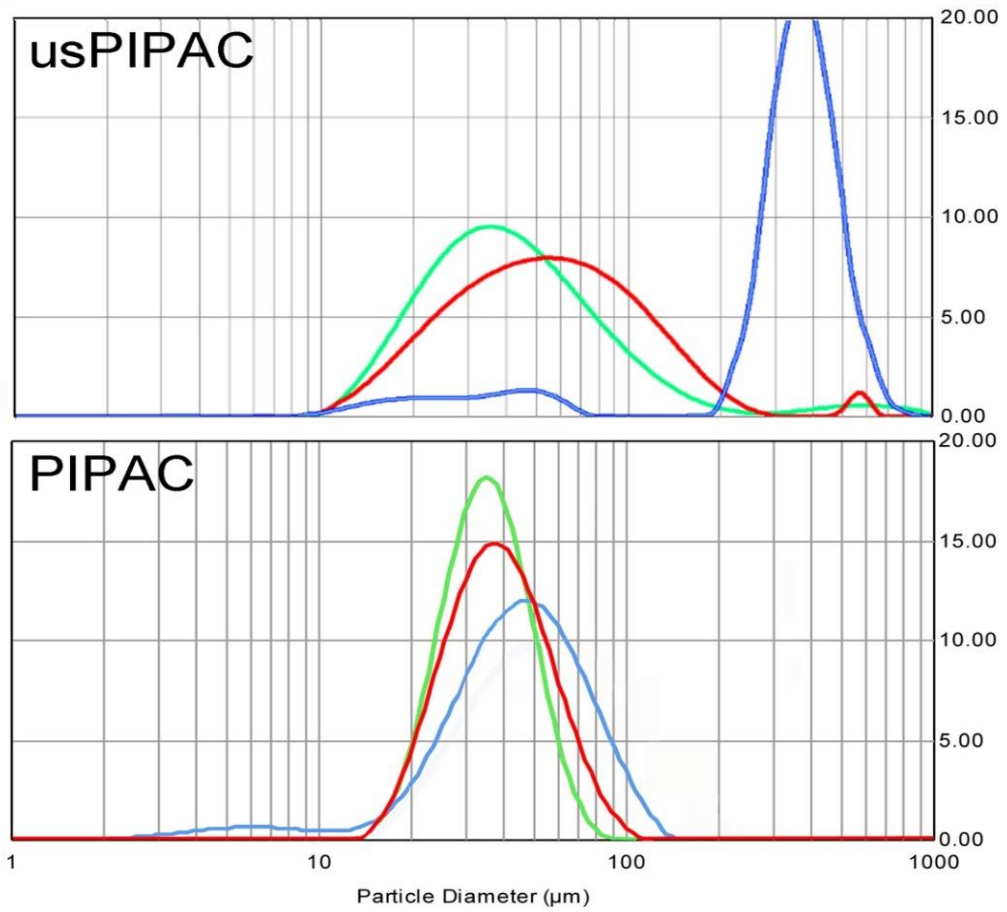


Hoeltzcke P et al, Surg Endosc (in press)

usPIPAC: granulometry

Granulometry of usPIPAC equivalent to PIPAC for aqueous solutions (green curve)

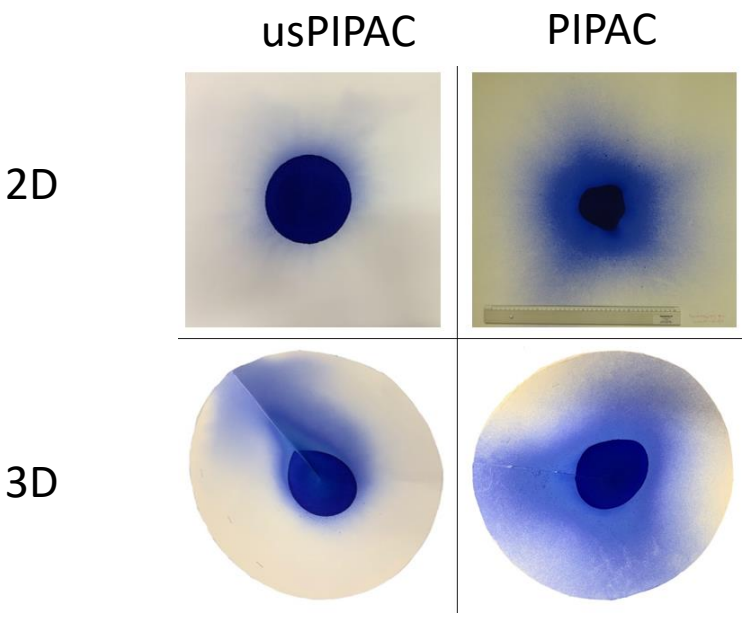
PIPAC superior for glucose (red) or silicone oil (blue)



Hoeltzcke P et al, Surg Endosc, in press

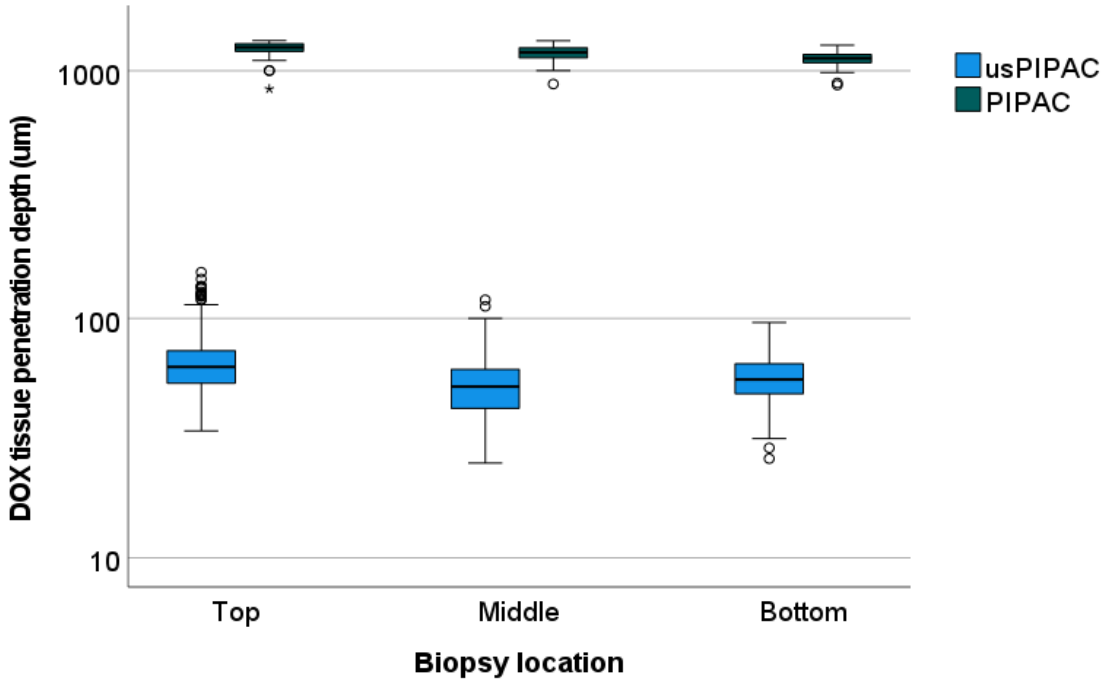
usPIPAC: spatial distribution, tissue penetration

Homogeneity of spatial distribution



Coverage after PIPAC superior to usPIPAC

Tissue penetration

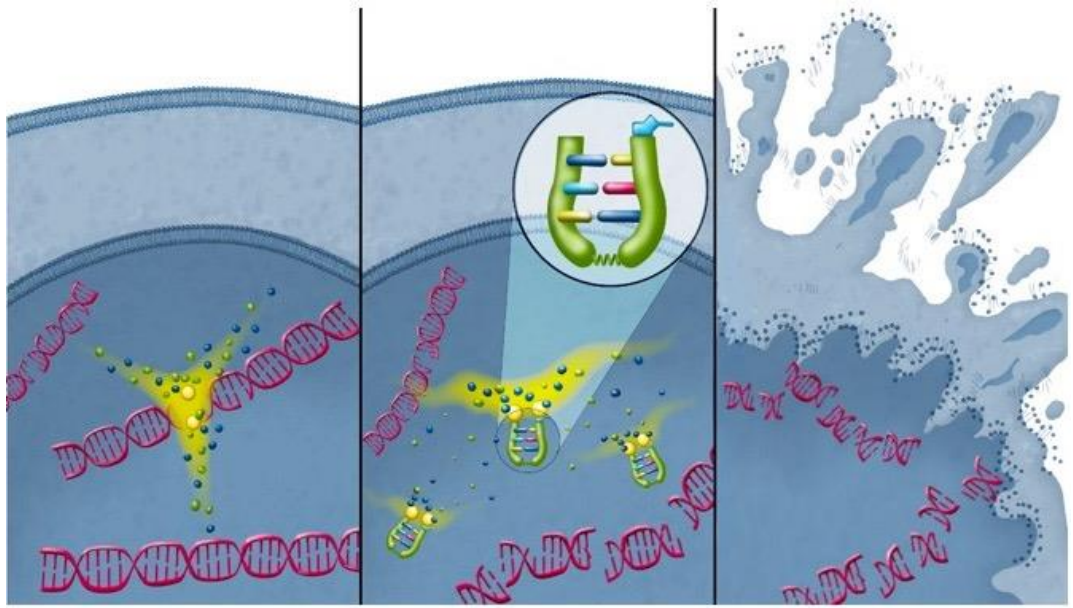


DOX depth of penetration after PIPAC superior to usPIPAC

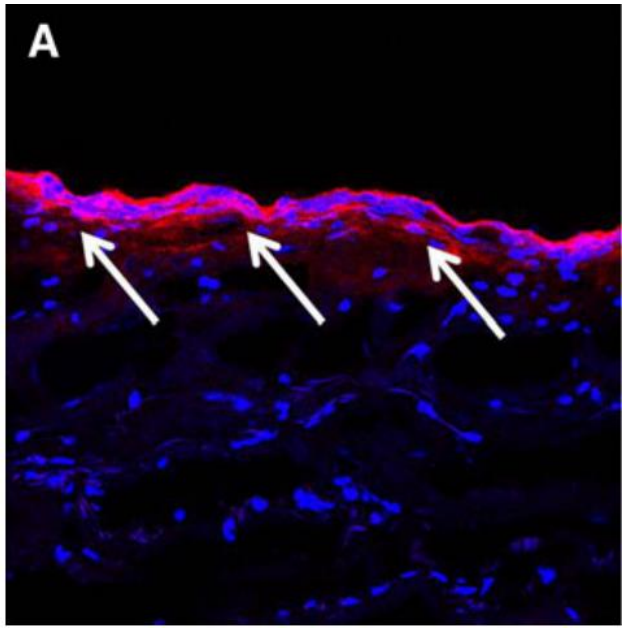
Hoeltzcke P et al, Surg Endosc, in press

PIPAC for non-viral gene delivery: siDNA

AsiDNA = **DNA damage repair inhibitor** disrupting and exhausting the tumour DNA damage response mechanism.



Onxeo-AsiDNA-cancer-treatment.jpg (669×490) (labiotech.eu)

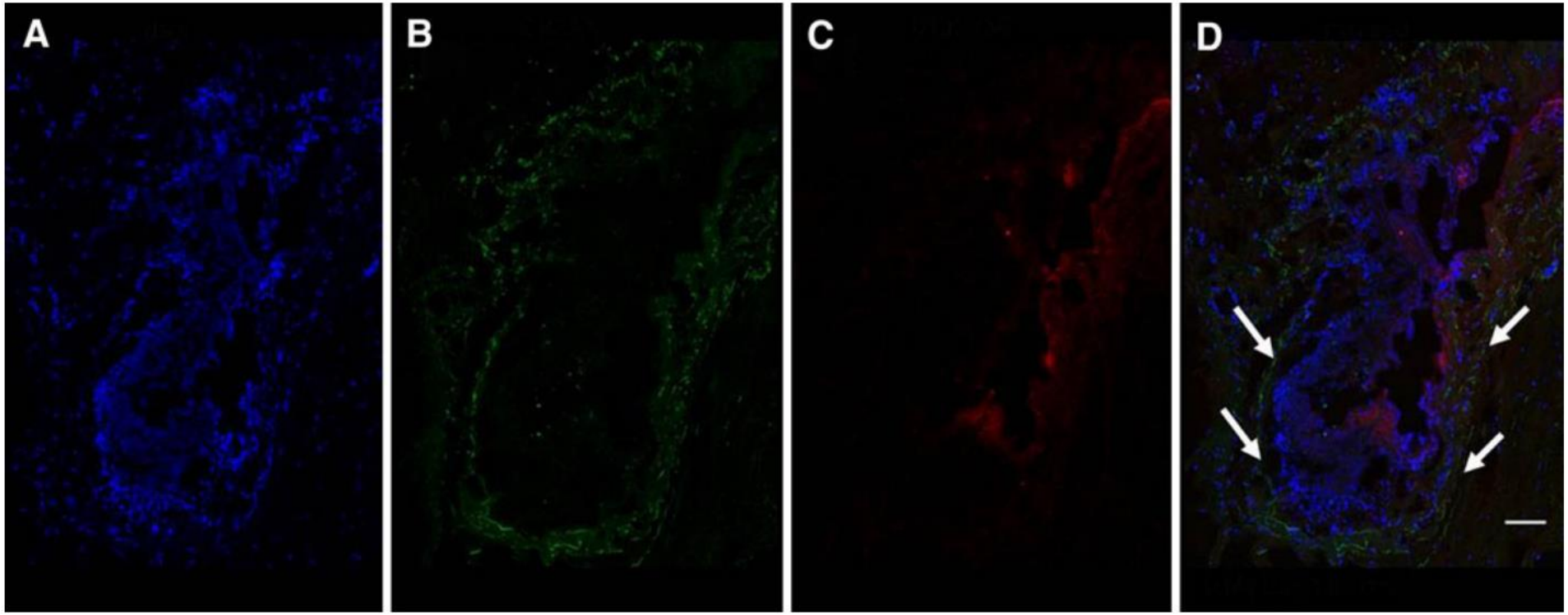


Dbait can be delivered as PIPAC into human peritoneal tissue

Solass et al Surg Endosc 2012

PIPAC for non-viral gene delivery: siDNA

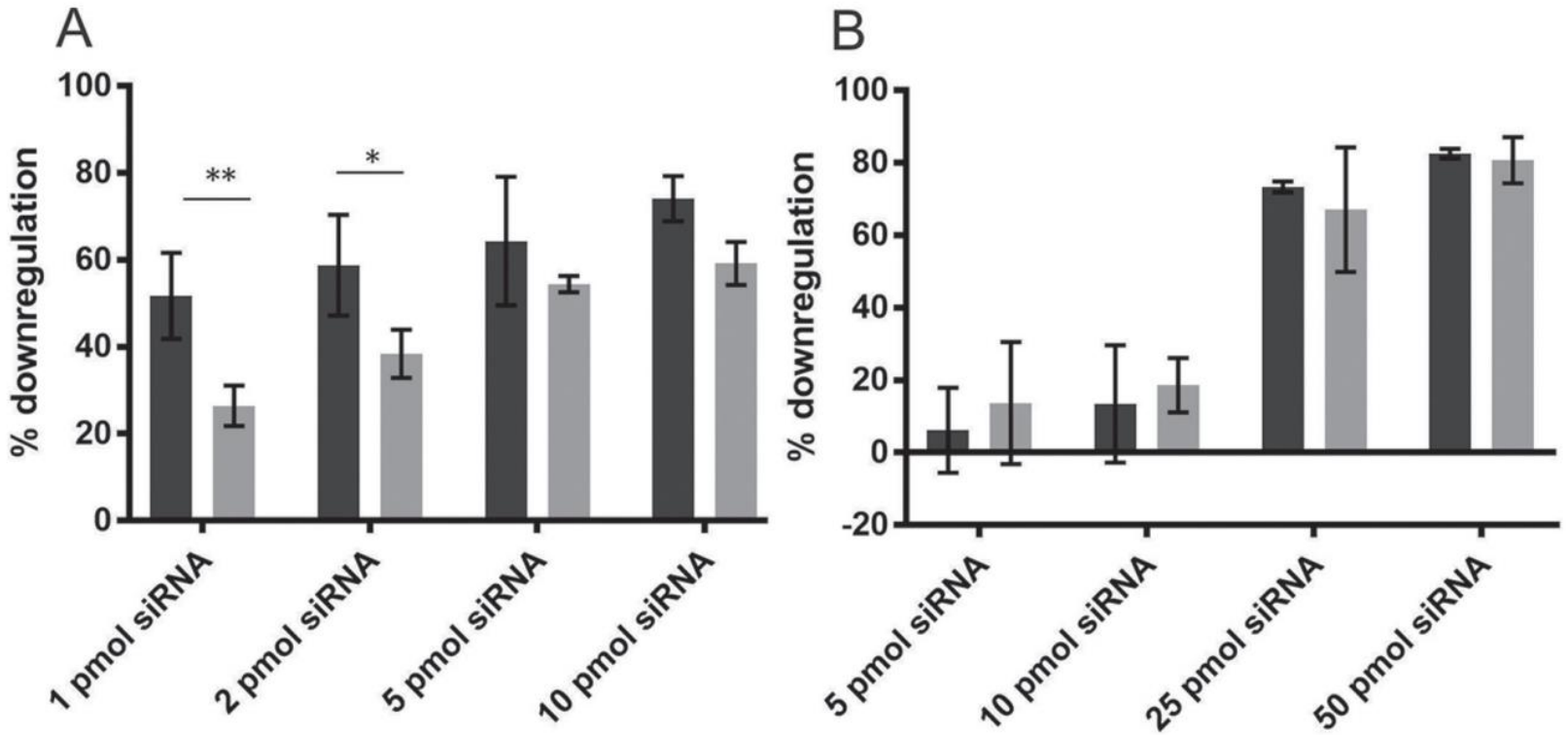
AsiDNA (as PIPAC) sensitizes human peritoneal cancer nodes to genotoxic therapy ex-vivo



Detection of histone gamma-H2AX (phosphorylatedH2AX) reveals nuclear activation of DNA-PK by AsiDNA

PIPAC for non-viral gene delivery: RNA lipoplexes

RNAiMAX/siRNA lipoplexes (N/P ratio 3) ADM70/siRNA complexes (N/P ratio 6)



Administration of RNA lipoplexes as PIPAC In vitro, nebulization of the siRNA complexes did not lower significantly transfection efficiency of SKOV3 cells when compared to non-nebulized complexes.

- Minnaert et al. Macromol Biosc 2017

PIPAC for non-viral gene delivery: RNA lipoplexes

Systemic route

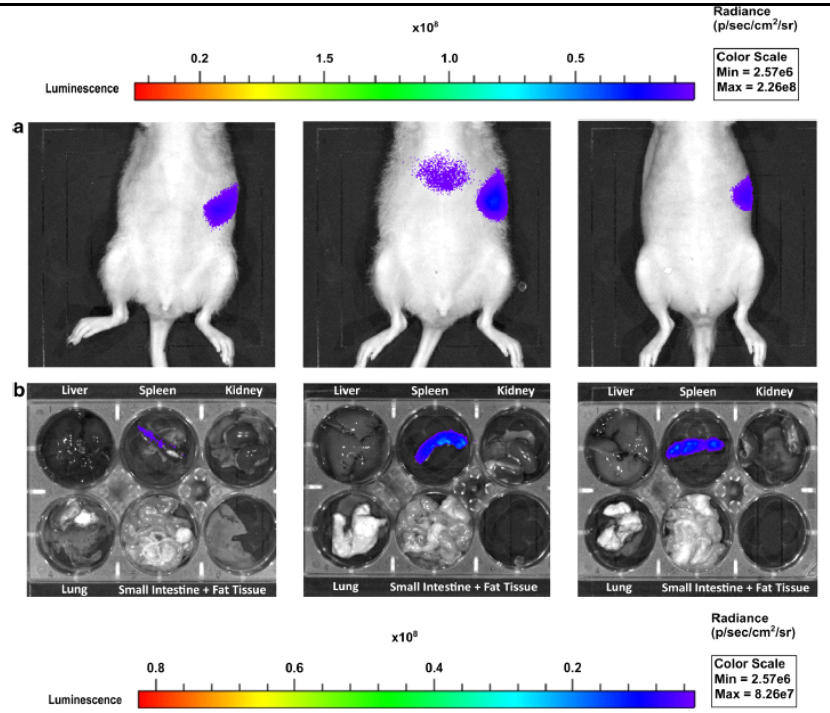


Fig. 3 Biodistribution of IV injected messengerMAX/mRNA lipoplexes in healthy nude rats. (**a**) Representative whole-body bioluminescence images and (**b**) *ex vivo* expression profile of rats at 4 h post-IV injection of messengerMAX/mRNA lipoplexes at a 25 μg dose.

Intraperitoneal route

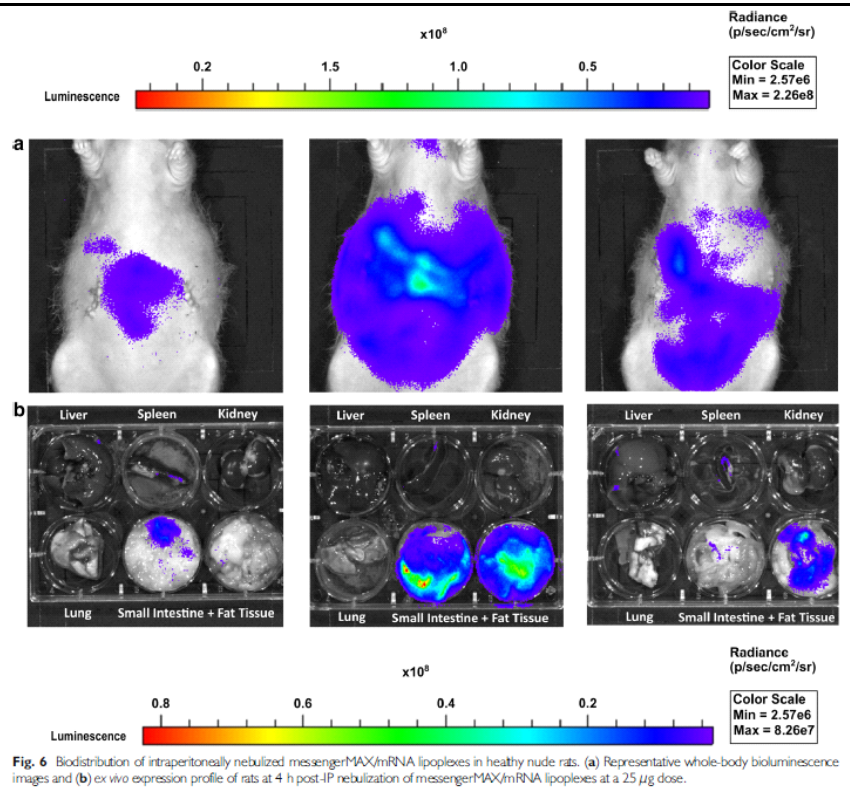


Fig. 6 Biodistribution of intraperitoneally nebulized messengerMAX/mRNA lipoplexes in healthy nude rats. (**a**) Representative whole-body bioluminescence images and (**b**) *ex vivo* expression profile of rats at 4 h post-IP nebulization of messengerMAX/mRNA lipoplexes at a 25 μg dose.

In-vivo, PIPAC distribution of RNA was superior to the IV route. Bioluminescence was localized to the peritoneal cavity, while IV injection mainly induced protein expression in the spleen.

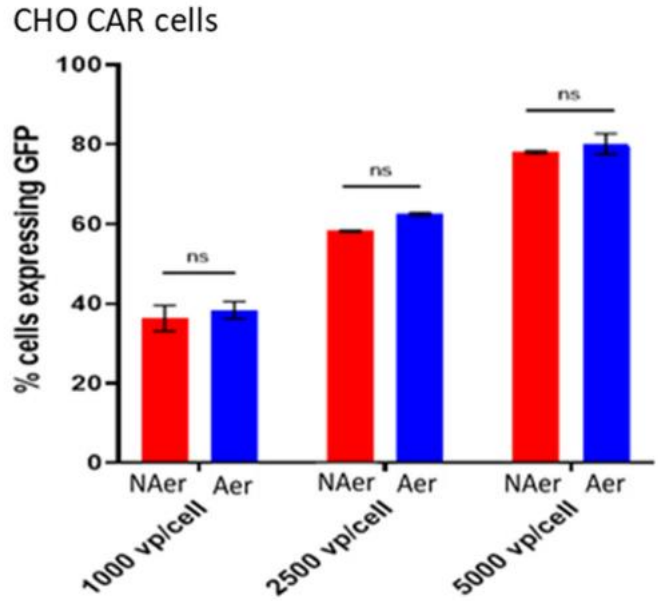
- Shariati et al, Pharm Res 2019

City of Hope

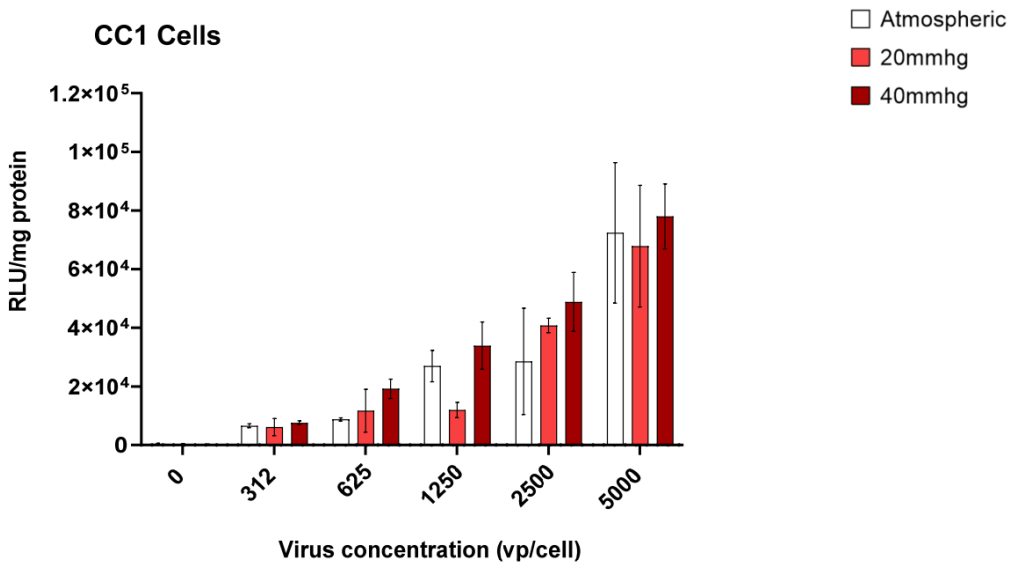
ISSPP

PIPAV: Pressurised Intraperitoneal Aerosolised Virotherapy

Demonstration of feasibility in vitro



Cytolytic adenovirus Ad5.GFP survives aerosolization using the CapnoPen device and retains its ability to transduce Wistar Rat hepatocytes in vitro



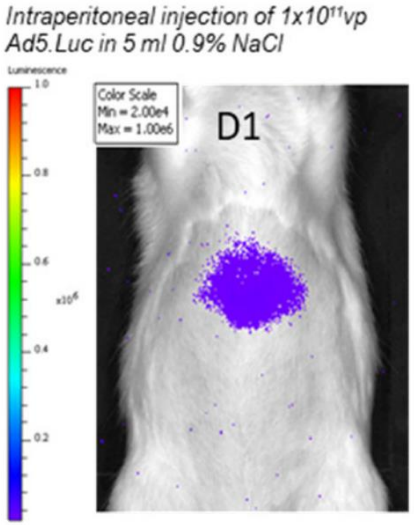
The virus is unaffected by exposure to hyperbaric conditions (up to 40 mmHg)

Tate et al, Pharmaceutics 2021

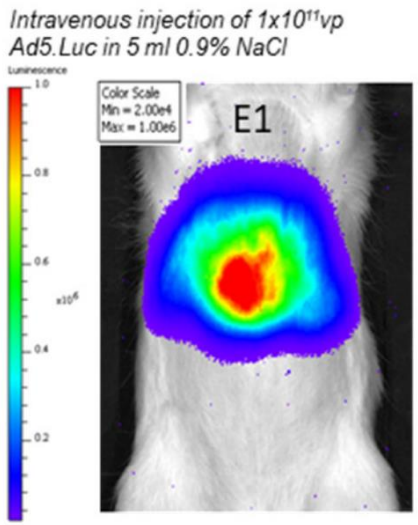
PIPAV: Pressurised Intraperitoneal Aerosolised Virotherapy

Demonstration of feasibility in-vivo (Wistar rat model)

Intraperitoneal



Intravenous



Luciferase expression 72 h after IV & IP injection (IVIS)

The higher luminescence in the IV group is likely due to viral expression in the liver & clotting factor X in the blood engaged by Ad5 to enter cells presenting Heparan Sulfate ProteoGlycans.

Treatment group	Rat	Day 0	Day 1 post procedure			Day 2 post procedure		
		Weight (g)	Weight (g)	% change	Analgesia	Weight (g)	% change	Analgesia
Intraperitoneal Ad5.Luc injection (3×10^{10}vp)	A1	343	345	0.6	0	350	1.4	0
	A2	335	337	0.6	0	343	1.8	0
	A3	349	352	0.9	0	353	0.3	0
Intraperitoneal Ad5.Luc aerosolisation (3×10^{10}vp)	B1	342	345	0.9	0	330	−4.3	1
	B2	330	330	0.0	0	307	−7.0	1
	B3	340	334	1.2	0	332	−0.6	1
Intraperitoneal 0.9% NaCl injection	C1	337	334	−0.9	1	337	0.9	0
Intraperitoneal 0.9% NaCl aerosolisation	C2	333	324	−2.7	1	317	−2.2	1
Intraperitoneal Ad5.Luc injection (1×10^{11}vp)	D1	345	342	0.0	0	350	0.0	0
Intravenous Ad5.Luc injection (1×10^{11}vp)	E1	345	344	0.0	0	347	0.0	0
Intraperitoneal 0.9% NaCl injection	F1	346	350	0.0	0	353	0.0	0

The rats tolerated the increased dose (1 × 1011 vp) well

No increase in welfare scores, no requirement for analgesia

Tate et al, Pharmaceutics 2021

Summary

- **Pressure** increases drug tissue uptake (by convection)
- **ePIPAC**
  - improves the homogeneity of spatial distribution vs. PIPAC
  - increases the depth of tissue penetration (DOX, PTX)
  - should be applied for at least 6 min, activation before aerosolization
- **hPIPAC** is feasible but has no pharmacological advantage over PIPAC in the eIBUB model
- **usPIPAC** is feasible but has no advantage over PIPAC in the eIBUB model
- PIPAC can be used for **non-viral (DNA, RNA)** and **viral (PIPAV) gene delivery**