

SOLID21

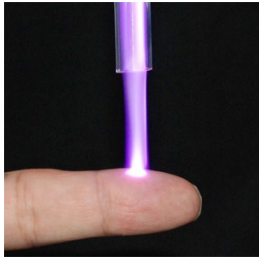
Research program 4 – “Physics for Bio”

RP leader:
Oleg Lunov, PhD

Physics for bio - Motivation

Physics-based biomedical approaches

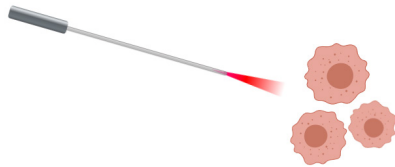
Non-thermal plasma



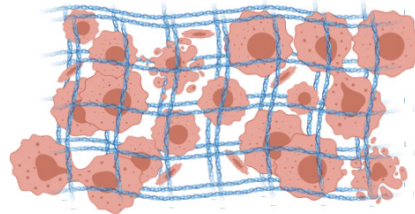
Transcranial magnetic stimulation



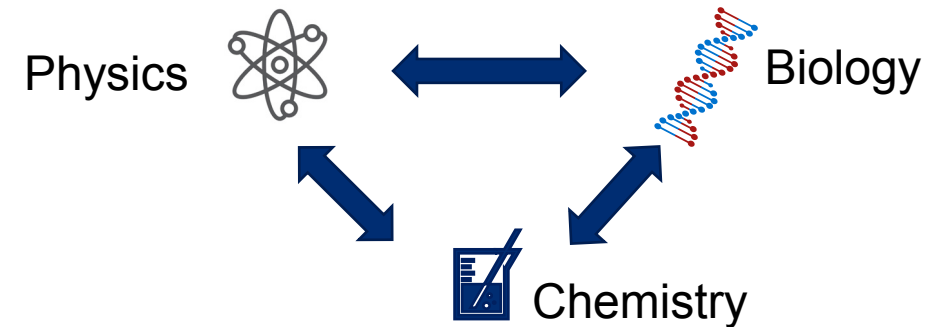
Photobiomodulation



Novel biomaterials



Interdisciplinarity is key for success!



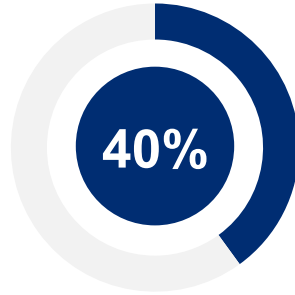
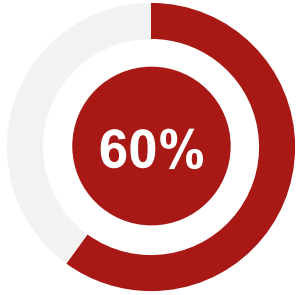
RP4 aims to create unique *interdisciplinary platform* that would merge complex research across physics, chemistry, biology, and medicine. Our goal is to gain deep insights in fundamental mechanistic understanding of selected physical factors.



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Akademie věd
České republiky

RP4 Infographics



Irena Kratochvílová, Ph.D.
leader of *RA4 - Nanoparticles*
for *theranostics*



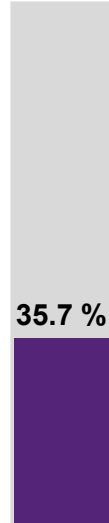
Hana Lísalová, Ph.D.
leader of *biosensors research*
direction



TAs



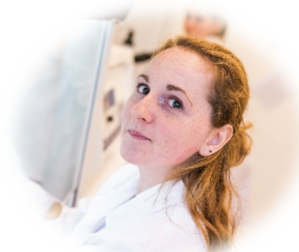
Students



Postdocs



Scientists



Barbora Smolková
defended 25. 5. 2022
Mobility program to Oslo University



Mariia Uzhytchak



Ekaterina Shagieva
defended 27. 5. 2022



Daria Miliiaeva



Petra Elblová

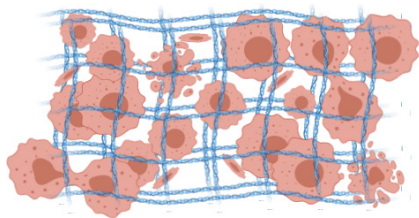


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“Physics for Bio” Research Activities (RA)

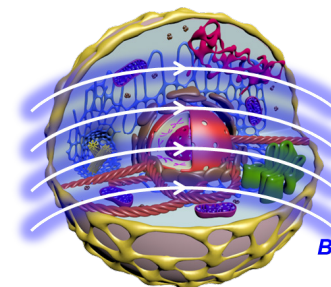
RA5 - Biomaterials and biointerfaces



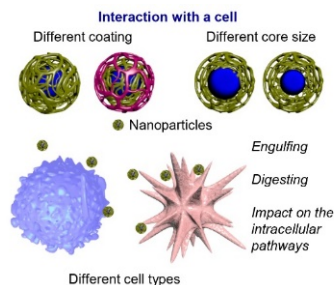
RA5 -
Potocký

RA1 -
Lunov

RA1 - Biophysics of high-gradient magnetic fields



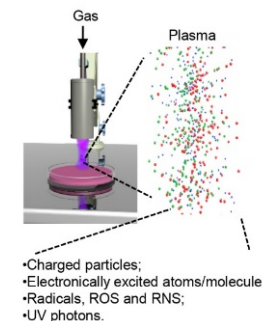
RA4 - Nanoparticles for theranostics



RA4 -
Kratochvílová

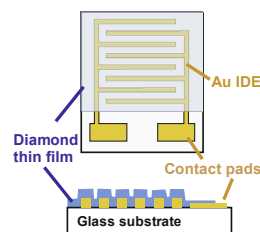
RA2 -
Dejneka

RA2 - Plasma and irradiation for bioapplications



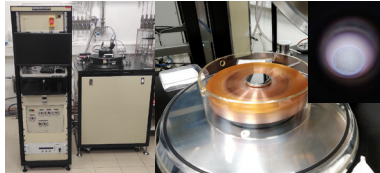
RA3 -
Kromka

RA3 - Bioelectronics and biosensors



Projected Final State and Timeline

ISAB critics and comments were very important.



Advancing
interdisciplinary
research



Expanding
international
visibility of the
program and active
interaction with
industrial partners



2018-2019

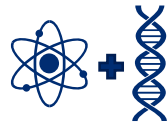
2020

2021

2022

2023

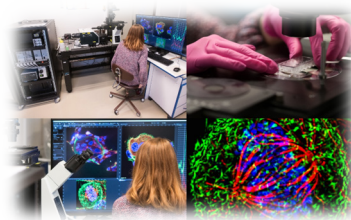
Developing
infrastructure and
networking of the
RP4 team



International
visibility of the
program



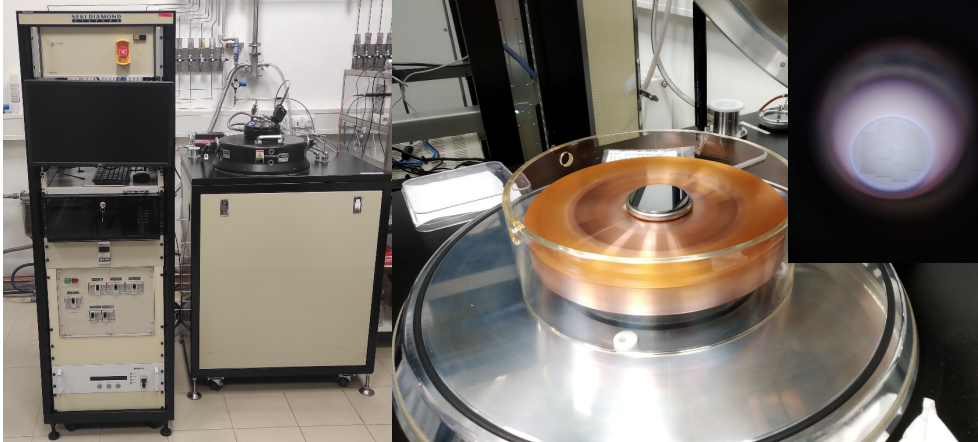
Interdisciplinary
platform
gain deep insights in
*fundamental
mechanistic
understanding* of
how selected physical
factors (e.g., magnetic
fields, non-thermal
plasma, various
nanoparticles,
diamond, or diamond-
like carbon
biomaterials) affect
biological systems.



Main Acquired Equipment and Infrastructure



Novel life super-resolution imaging system



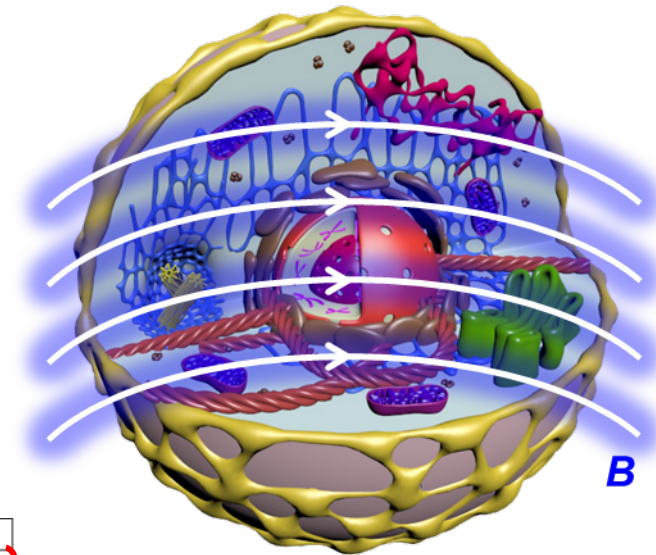
*Microwave plasma deposition system
SDS6K, Seki Diamond Systems Ltd.*



New laboratories & offices

Results RA1

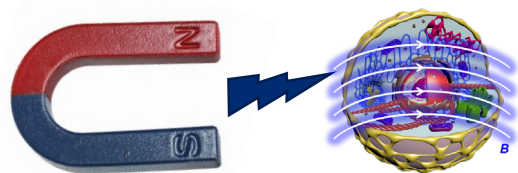
Biophysics of high-gradient magnetic fields (Lunov)



RP 4		2018	2019				2020				2021				2022				2023		
		IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III
RA1	WP1	Effects of HGMF on magnetic nanomaterials						M4.01													
	WP2	Static and pulsed HGMFs effects on stem cell functionality										M4.02									
	WP3	Study of cell behavior on magnetically patterned substrates										M4.03									
	WP4	Effects of HGMFs on membrane potential of cells										M4.04									
FTE		0.76	3.00				3.00				3.00				3.00				2.39		

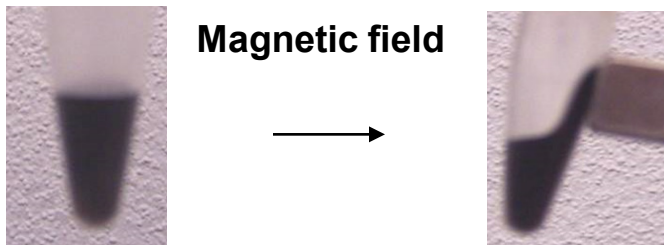
Progress Since the Start of the Project and Since the last ISAB

MAGNETIC MATERIALS



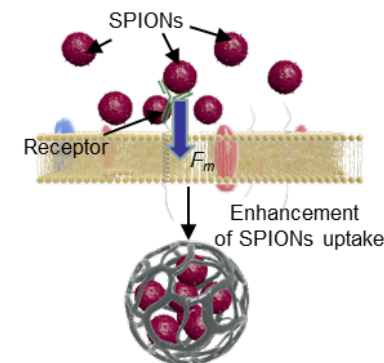
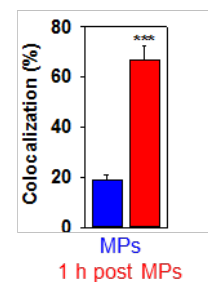
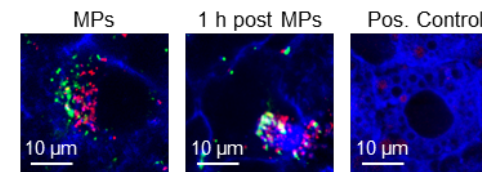
Biological effects

mechanisms induced by external magnetic fields

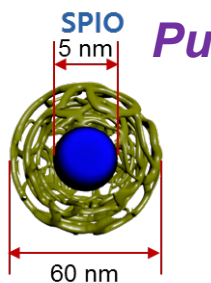


Magnetic field

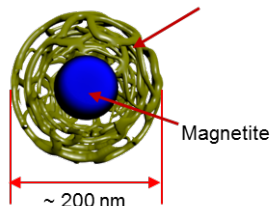
Endocytosis



Dr. Nora M. Dempsey
Institut Neel,
CNRS/UJF, Grenoble

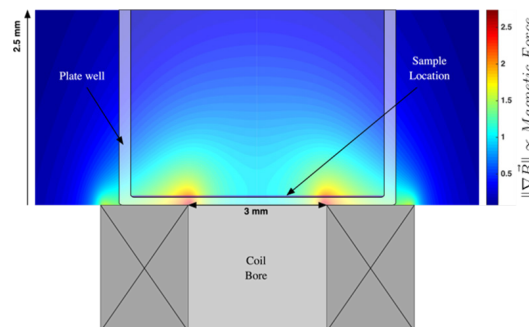


Carboxymethyldextran

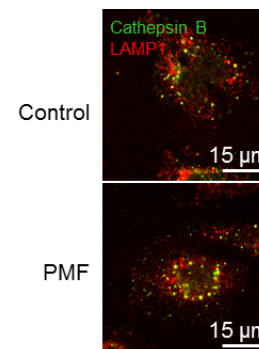


Magnetite

Pulsed magnetic field ~ 7-8 T

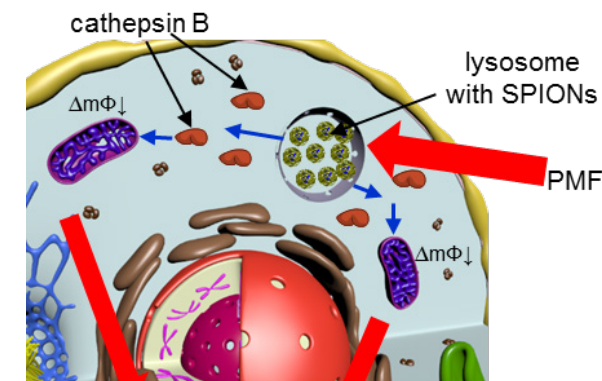


Cancer killing



SPIONs

SPIONs + PMF



APOPTOSIS



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Uzhytchak et al, *Appl Phys Lett.* 2017; 111: 243703.
Lunov et al, *Cancers* 2019; 11: 1873.

Milestones and Deliverables

Effects of HGMF on magnetic nanomaterials



Contradictory Results

Follow this preprint

No evidence for detectable direct effects of magnetic field on cellular autofluorescence

Static and pulsed HGMFs on cells



Mariia Uzhytchak, Barbora Smolková, Adam Frtús, Alexandr Stupakov, Mariia Lunova, Federica Scollo, Martin Hof, Piotr Jurkiewicz, Gareth John Sullivan, Alexandr Dejnek, Oleg Lunov

doi: <https://doi.org/10.1101/2022.05.15.491784>

Study of cell behavior under magnetic field

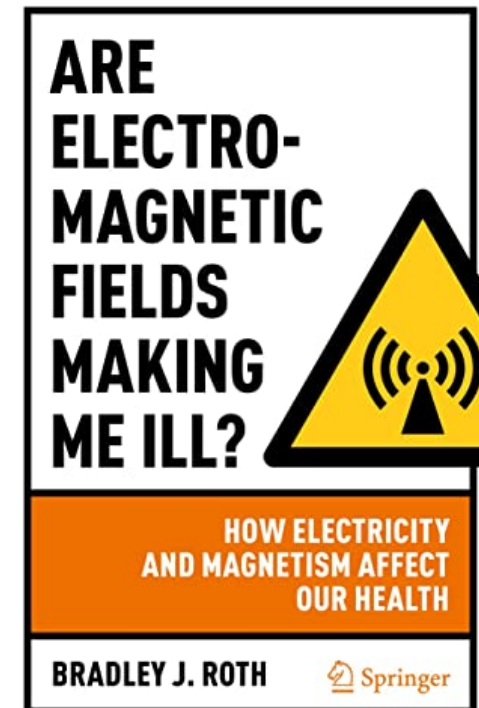


This article is a preprint and has not been certified by peer review [what does this mean?].

Effects of HGMFs on membrane potential



The results show that the predicted effects are too weak to account for the reported measurements by huge margins: between **five and ten orders of magnitude**.



Future Plans and Risks (Sustainability)



*Dr. Nora M. Dempsey
Institut Neel,
CNRS/UJF, Grenoble*

Continue and expand cooperation within created cluster of RP4 (RA3,4,5)

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Matthew J Page,¹ Joanne E McKenzie,¹ Patrick M Bossuyt,² Isabelle Boutron,³ Tammy C Hoffmann,⁴ Cynthia D Mulrow,⁵ Larissa Shamseer,⁶ Jennifer M Tetzlaff,⁷ Elie A Akl,⁸ Sue E Brennan,¹ Roger Chou,⁹ Julie Glanville,¹⁰ Jeremy M Grimshaw,¹¹ Asbjørn Hróbjartsson,¹² Manoj M Lalu,¹³ Tianjing Li,¹⁴ Elizabeth W Loder,¹⁵ Evan Mayo-Wilson,¹⁶ Steve McDonald,¹ Luke A McGuinness,¹⁷ Lesley A Stewart,¹⁸ James Thomas,¹⁹ Andrea C Tricco,²⁰ Vivian A Welch,²¹ Penny Whiting,¹⁷ David Moher²²

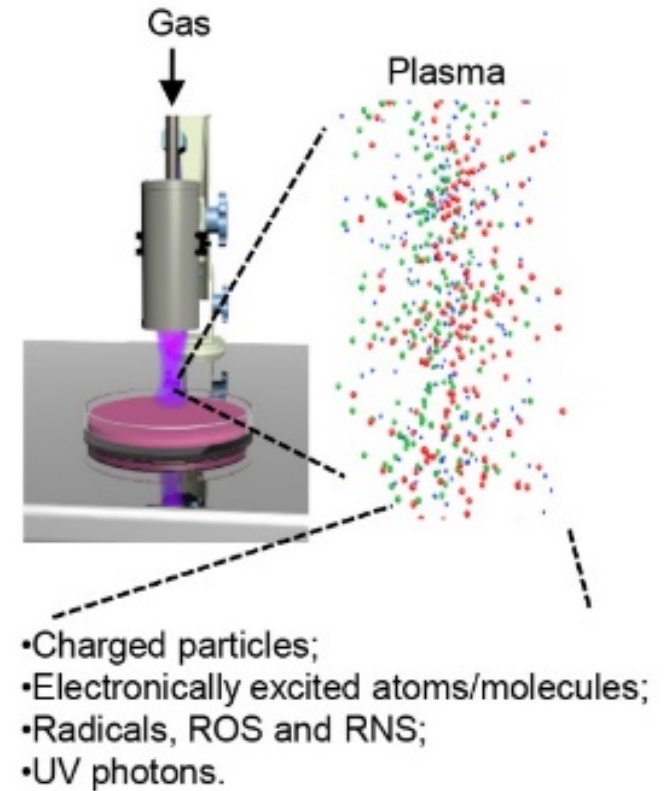
Critical systematic review of current literature

Expanding international visibility and cooperation

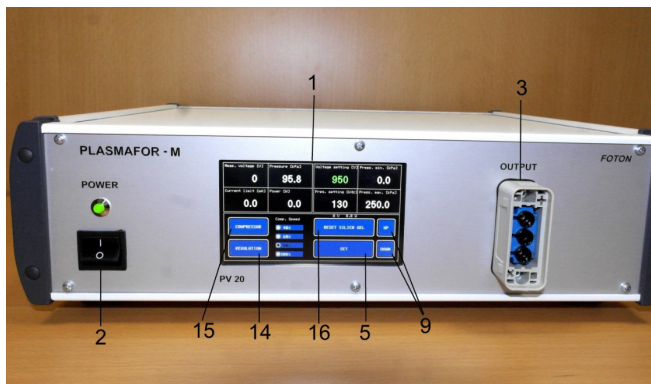
Results RA2

Plasma and Irradiation for Biomedicine (Dejneka)

RP 4		2018	2019				2020				2021				2022				2023		
		IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III
RA2	WP1	Physicochemical analysis of non-thermal plasmas M4.05																			
	WP2	Effects of non-thermal plasmas on distinct cell cultures M4.06																			
	WP3	Immunomodulatory effects of non-thermal plasma M4.07																			
	WP4	Effects of NTP treatment on wound healing processes M4.08																			
FTE		0.52	2.00				2.00				2.00				2.00				1.56		

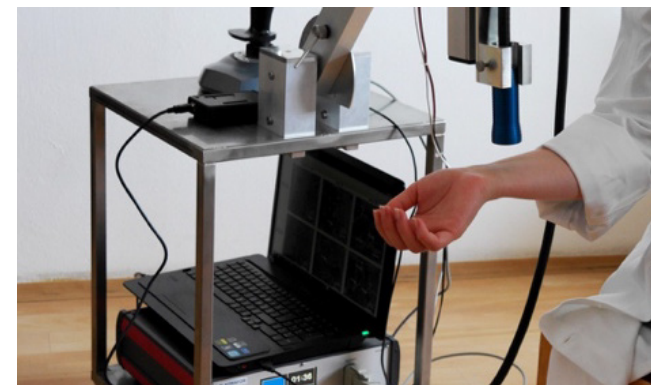


Progress Since the Start of the Project and Since the last ISAB



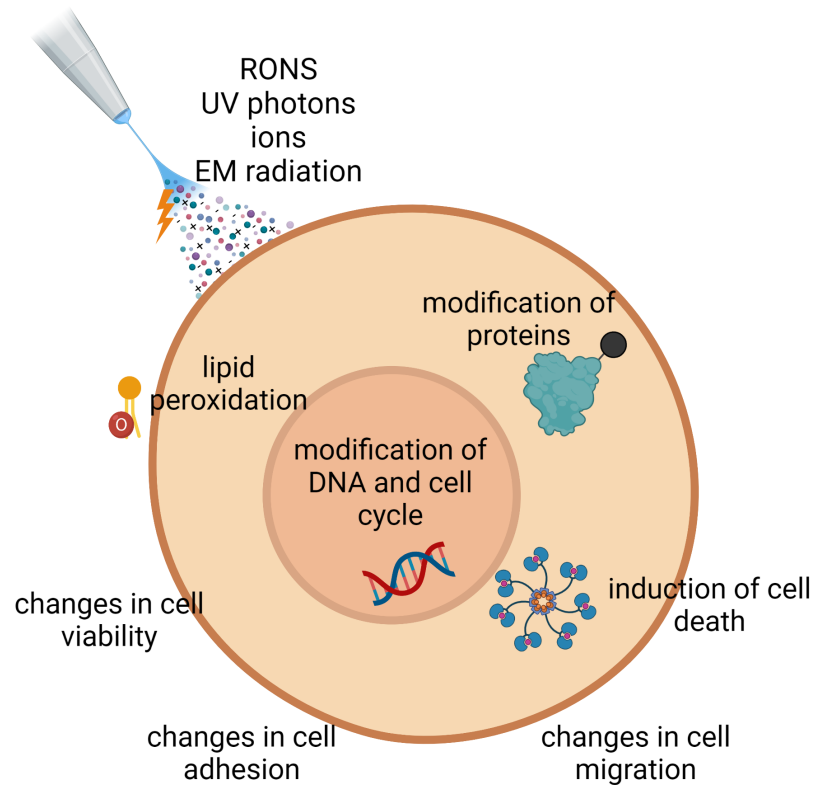
Cold plasma generator certified for veterinary use. Pilot testing was done in 21 contractual veterinary clinics

In the evaluation period, construction of the plasma nozzle was protected by 1 patent and 2 utility models.



Clinical study for human medicine applications was started at the Burn medical center in Brno

Milestones and Deliverables



Lunov et al, *Appl Phys Lett* 2015; 106: 053703.

Lunov et al, *Sci Rep* 2014; 4: 7129.

Lunov et al, *Br J Dermatol* 2016; 174: 486.

Lunov et al, *Biomaterials* 2016; 82: 71.

Lunov et al, *Sci Rep* 2017; 7: 45183.

Lunov et al, *Sci Rep* 2017; 7: 600.

Smolkova et al, *Cell Physiol Biochem* 2019; 52: 119.

Smolkova et al, *Int J Mol Sci* 2020; 21: 6226.

Smolkova et al, *Cancers* 2021; 13: 4549.

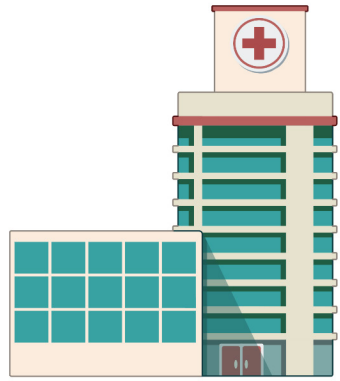
Physicochemical characterization of NTP ✓

NTP effects on living cells ✓

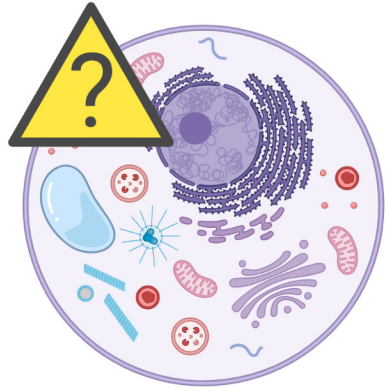
Immunomodulatory effects of NTPs ✓

Wound healing by NTPs ✓

Future Plans and Risks (Sustainability)



Poor clinical transition



Unknown molecular mechanism

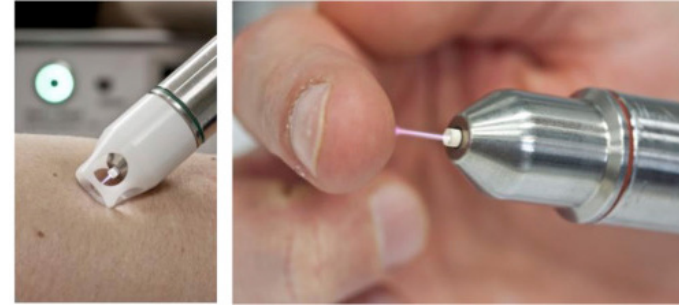


Questionable animal and cellular models



Missing standardisation

CE certification (kINPen MED)



Clin Plasma Med 4, 19-28 (2016).

FOTON, s.r.o.
SINDAT spol. s.r.o.
Agriculture and Food Industry

Institute for Clinical & Experimental Medicine (IKEM)



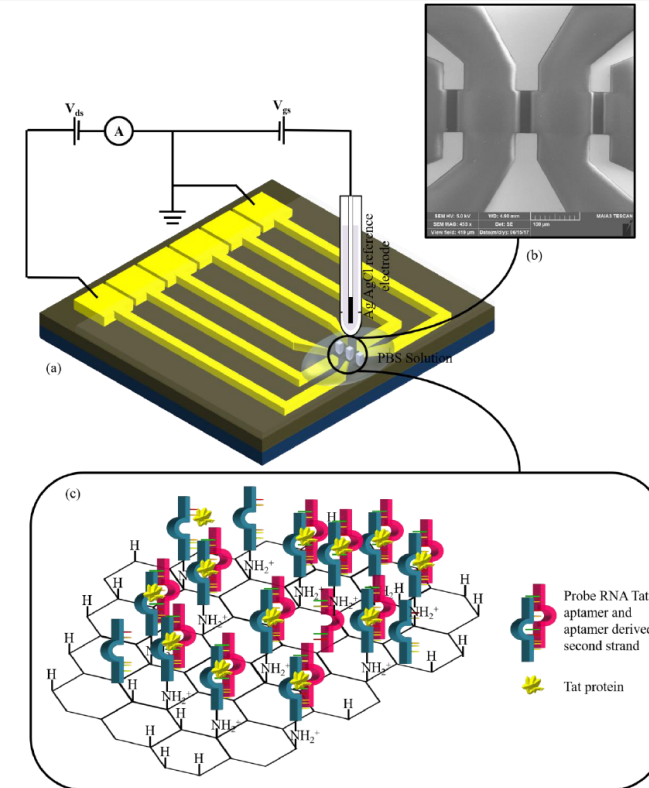
Burn medical center in Brno
University of Oslo, Norway

Smolková et al, *J Funct Biomater*. 2019; 10: 2.
Smolková, et al., *Int. J. Mol. Sci.*, 2020. 21: 17.

Results RA3

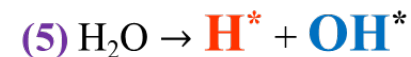
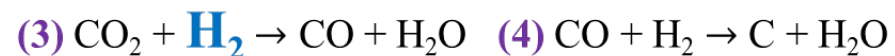
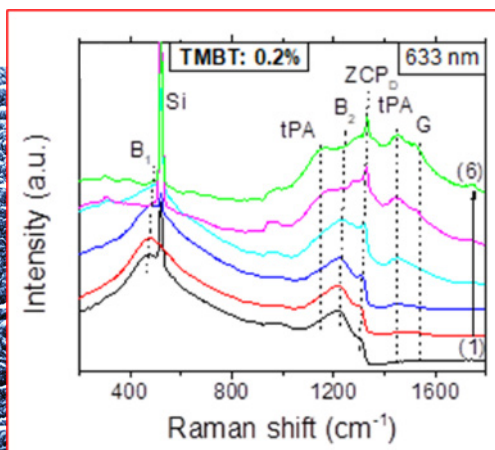
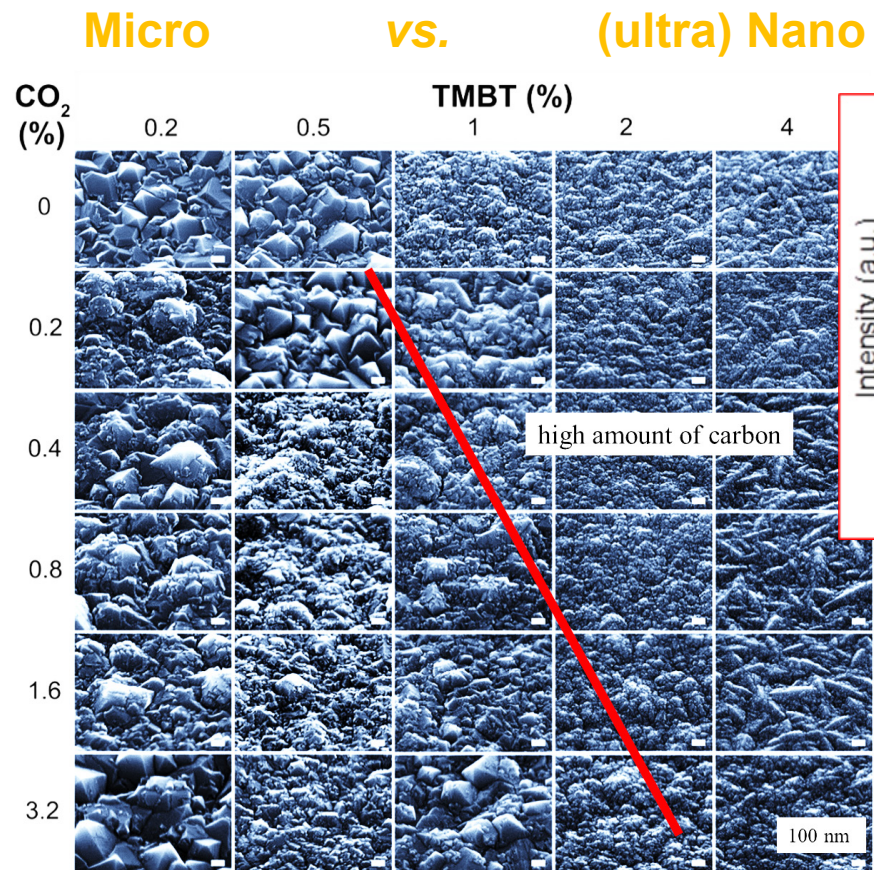
Bioelectronics and Biosensors (Kromka)

RP 4		2018	2019				2020				2021				2022				2023		
		IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III
RA3	WP1	Diamond and carbon based biodevices						M4.09													
	WP2	Optimization of technologic processes										M4.10									
	WP3	Interaction of cells with diamond/carbon surfaces						M4.11													
	WP4	Data validation and new approaches						M4.12													
FTE		0.86	3.40				3.40				3.40				3.40				2.76		

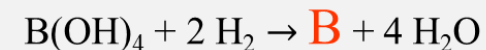
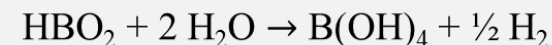
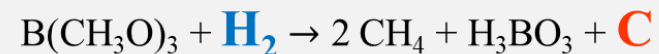


Progress Since the Start of the Project and Since the last ISAB

New chemical pathway for large-area deposition of doped diamond



pathways for active **C** and **B** atoms



*N. Makuch et al., Coatings. 10 (2020) 564

Boron-doped diamond grown **only from trimethyl borate** and **hydrogen** (no methane).

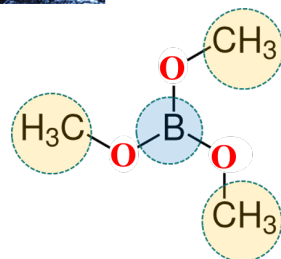
Boron doping level & morphology controlled by adding CO₂.

Trimethyl borate found as low-cost and safe liquid source for large-area MWCVD growth of doped diamond films!



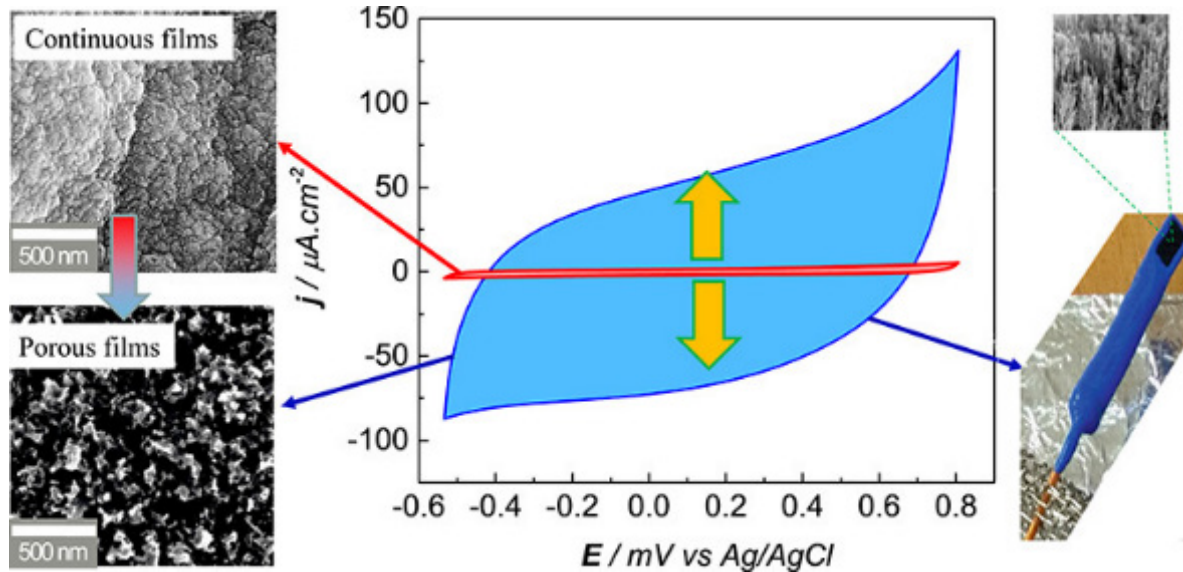
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Milestones and Deliverables

Novel Class of Nanoporous Diamond (Electrodes ...)



Štenclová et al., *Vacuum* 2019; 170: 108953

Ahmad et al., *Int. Jour. Nanoelectronics & Materials* 2020; 13: 295

Ukrainsev et al., *Carbon* 2021; 176: 642

Kočí et al., *Sensors* 2021; 21: 5390

J. Fait et al., *Applied Surface Sciences* 2019; 480: 1008

Ondič et al., *Nanoscale* 2020; 12: 13055

Fait et al., *Nanophotonics* 2021; 10: 1

Artemenko et al., *Diam. Relat. Mater.* 2019; 100: 107562

Procházka et al., *Colloids and Surfaces B: Biointerfaces* 2019; 177: 130

Krátká et al., *Colloids & Surf. B: Biointerfaces* 2021; 204: 111689

Procházka et al., *Applied Surface Science* 2022; 589: 153017

Varga et al., *ACS Omega* 2019; 4: 8441

Tulic et al., *RSC Advances* 2020; 10: 8224

Marton et al., *Diam. Relat. Mater.* 2022; 126: 109111

Pfeifer et al., *ACS App. Eng. Mat.* 2023; 1: 1446

...work in progress...

Diamond sensor (FETs & impedance & QCM devices) (M4.09) ✓

Novel opto-electronic devices (M4.10) ✓

Bio-interaction of cells with diamond (M4.11) ✓

Directions/concepts for biosensors (M4.12) ✓

Future Plans and Risks (Sustainability)

- ❑ Continue and expand cooperation within created cluster of RP4 and other partners



GERMANY

Photonics
Optical centers

Prof. M. Agio

Project to be submitted in 6/2023



INDIA

Supercapacitors Csp2/sp3
Dr. K. J. Sankaran

New project from 2023

- ❑ Expanding international visibility and cooperation



POLAND

Biosensors

Prof. R. Bogdanowicz

New project from 2023



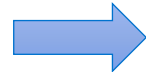
BELGIUM

Electrochemistry

Prof. N. Yang

Proof-of-concept experiments

- ❑ Critical systematic review of current state of the art



Massachusetts
Institute of
Technology

USA

Diamond NEMS

Prof. Ju Li

Proof-of-concept experiments

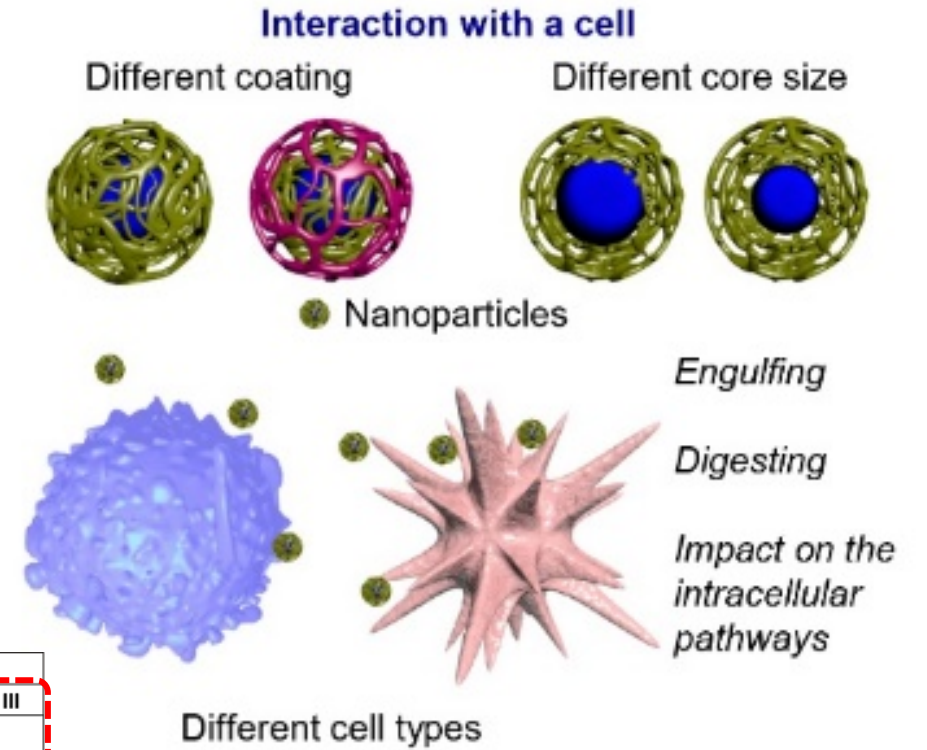
Project preparation
with the USA partner



Results RA4

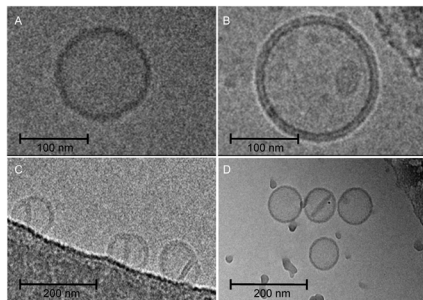
Nanoparticles for Theranostics (Kratochvílová)

RP 4		2018	2019				2020				2021				2022				2023		
		IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV			
RA4	WP1	Nanoparticles preparation						M4.13													
	WP2	Nanoparticles surfaces termination										M4.14									
	WP3						Tests of nanoparticles in cells								M4.15						
	WP4										Best nanoparticles properties determination/testing									M4.16	
FTE		0.47	2.40				2.40				2.40				1.90				1.52		

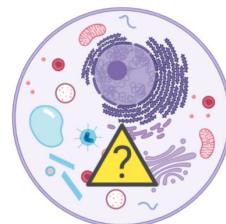
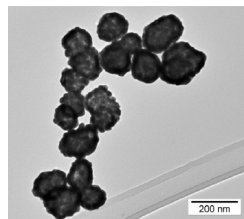


Progress Since the Start of the Project and Since the last ISAB

Liposomes



Magnetic nanoparticles



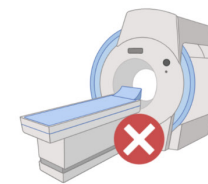
Unknown molecular mechanism



Cytotoxicity



Low tumor delivery in human



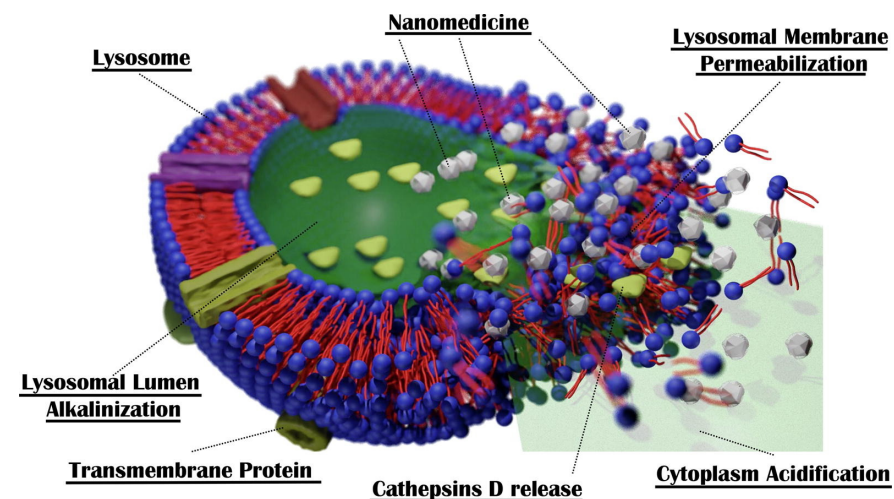
Poor clinical performance



Clinical failure

Frtús et al, *J. Control. Release* 2020; 328: 59.

Nowadays, there are **29** (**51** were in 2016) FDA-approved nanomedicines and **75** products in clinical trials.



Prospective European Drug-induced Liver Injury Network

28 Countries

Action COST CA17112

PRO-EURO-DILI-NET

Prospective European Drug-Induced Liver Injury Network

<https://proeurodilinet.eu/>

<https://www.cost.eu/actions/CA17112/#tabs|Name:overview>



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Nanoparticle-induced dysregulation of lysosomes as the main reason for nanotoxicity ²⁰

Uzhytchak et al, *Adv. Drug Deliv. Rev.* 2023; 197: 114828.

Milestones and Deliverables

- ✓ Nanoparticles preparation
- ✓ Nanoparticles surfaces termination
- ✓ Tests of nanoparticles in cells/
- ✓ Best nanoparticles determination / testing

NANOPARTICLES

- **Metallic nanomaterials** superparamagnetic iron oxide nanoparticles, gold, silver nanoparticles
- **Carbon-based nanomaterials** graphene, carbon nanotubes, nanodiamonds)
- **Polymer-based nanomaterials** / liposomes - phospholipids and cholesterol - spherical vesicles with a unilamellar or multivesicular lipid bilayer structure.

Unknown :

Chronic hepatotoxicity studies of NPs are needed.

Hepatotoxic effects caused by NPs have been observed in recent studies but have not been linked to liver disease, and the intrinsic mechanisms are poorly elucidated.

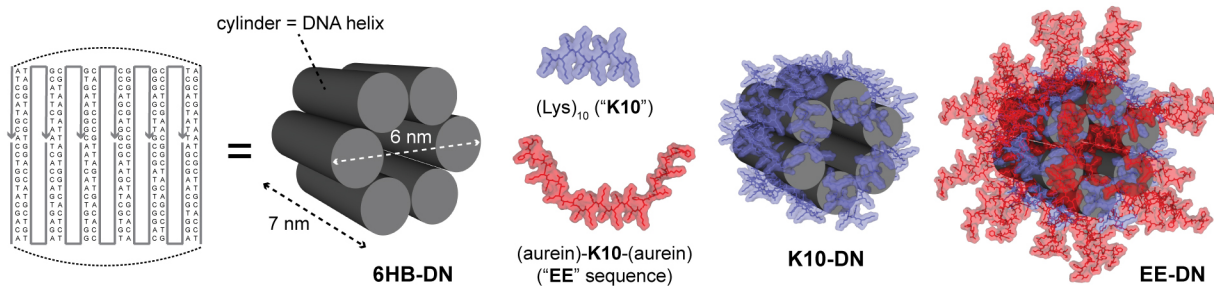
The toxic effects in susceptible livers (e.g. *NAFLD, NASH, fibrosis, cirrhosis*), and this issue has been ignored in current studies.

Future Plans and Risks (Sustainability)

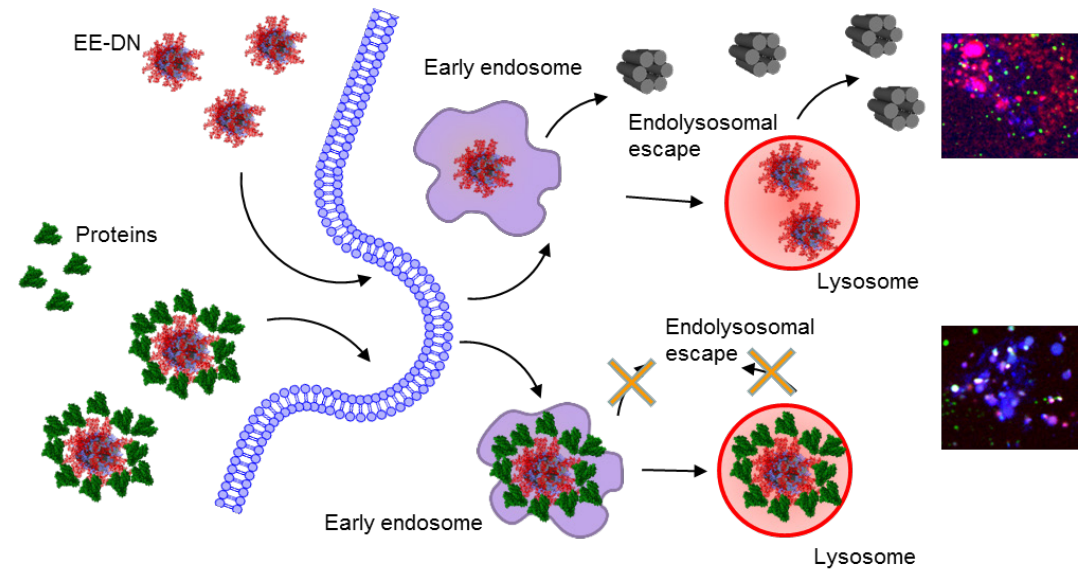
Towards more efficient combination of both therapy and diagnostics

FUTURE PLANS

- preparation of liposomes and lipid-based nanoparticles by on-chip technologies – vaccination constructs (cooperation with Czech company BIOVETA)
- preparation of terminated nanodiamonds and magnetic nanoparticles as cores for various complex theranostic nanosystems



Prof. Nicholas
Stephanopoulos
Arizona State University,
United States

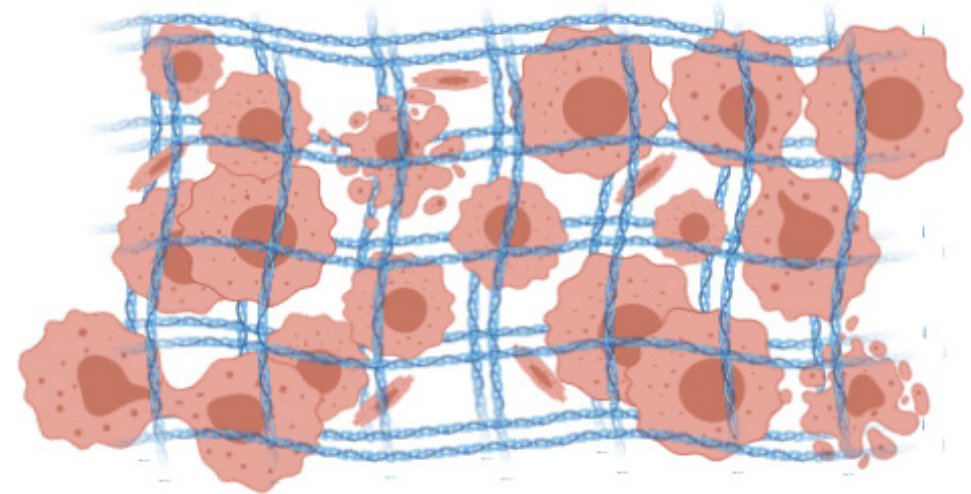


Frtús et al, *Acta Biomater.* 2022; 146: 10.

Smolková et al, *ACS Appl. Mater. Interfaces* 2021; 13: 46375.

Results RA5

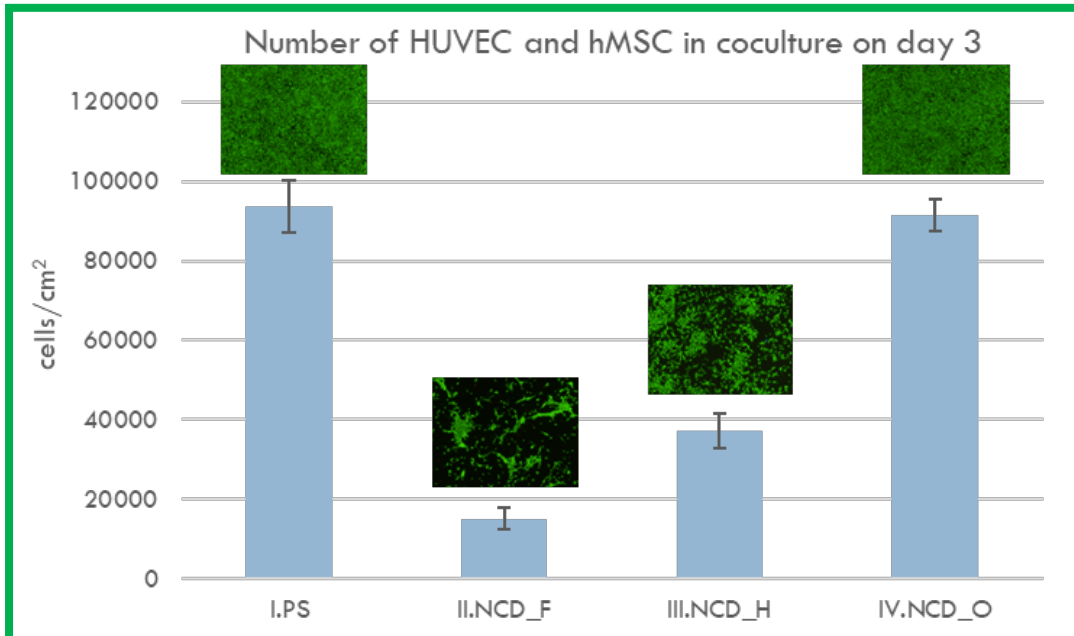
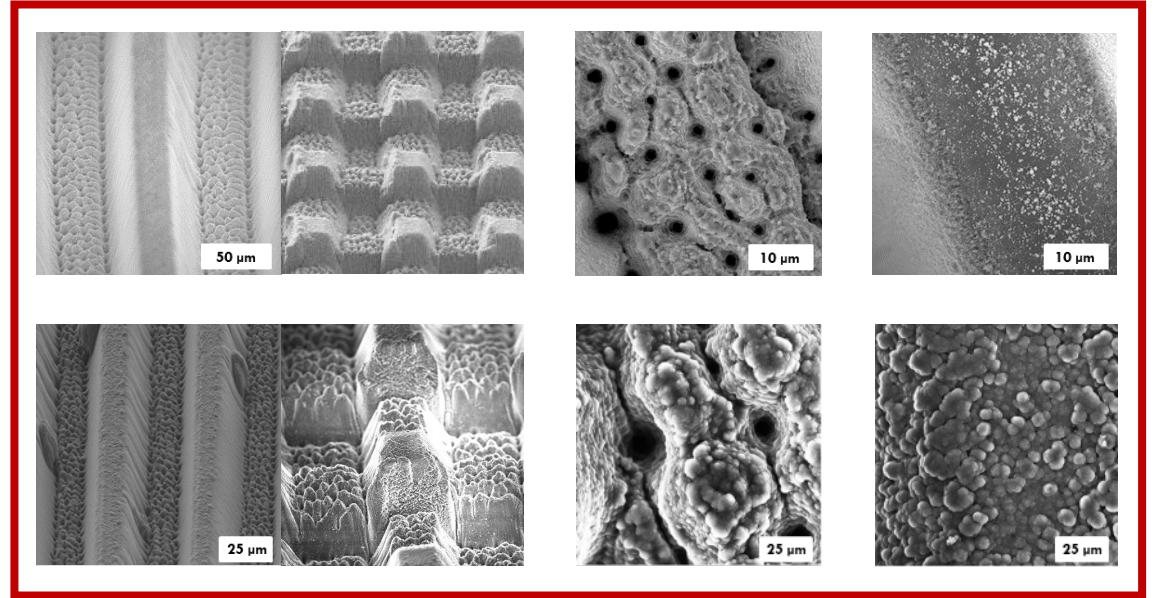
Biomaterials and Biointerfaces (Potocký)



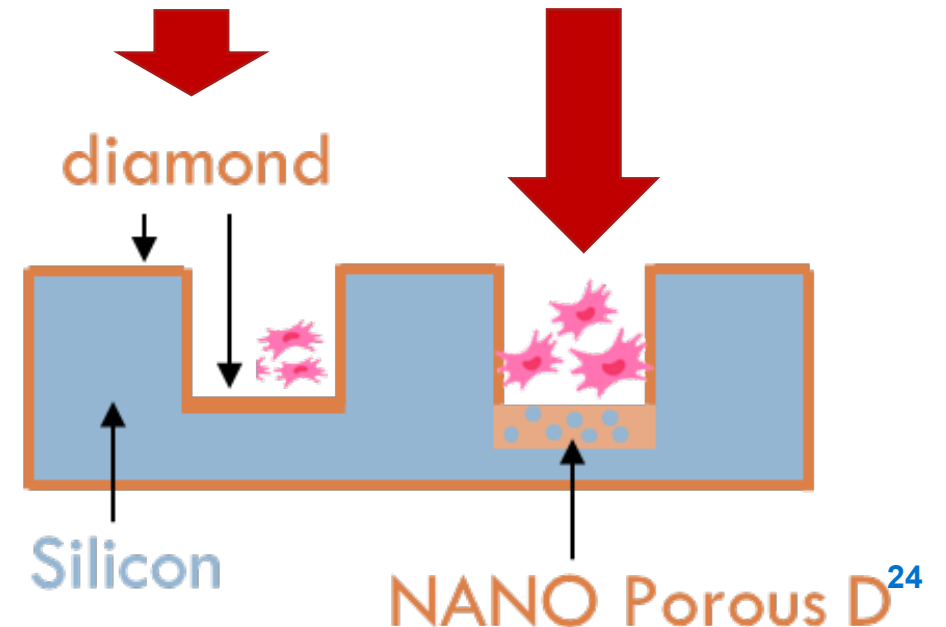
RP 4		2018	2019				2020				2021				2022				2023		
		IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV			
RA5	WP1	Fabrication of soft and hard artificial substrates M4.17																			
	WP2	Studies on cell cultivations on various surface morphologies/topographies M4.18																			
	WP3	Surface functionalization and cell experiments M4.19																			
	WP4	Establishing protocols & developing intelligent ECM M4.20																			
FTE		0.63	2.50				2.60				2.90				2.90				2.36		

Progress Since the Start of the Project and Since the last ISAB

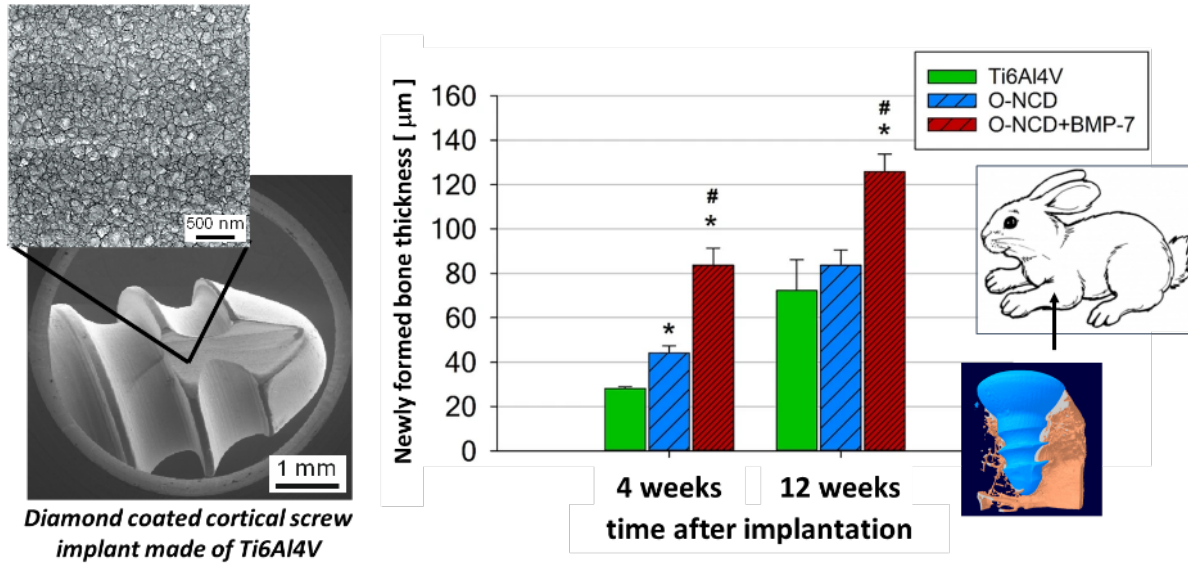
- ❑ Three-dimensional F-, H- and O- surface terminated **diamond-coated reservoirs** for cell cultures.
- ❑ Experiments with **monocultures** of *endothelial* and *mesenchymal stem cells* and their **co-culture**.
- ❑ Target – **highly vascularized bone tissue**.
- ❑ The cell culture protocol (M4.20).



Proliferation
&
colonization
experiments



Milestones and Deliverables



Mortet et al, *Carbon* 2020; 168: 319.
 Ondic et al, *Nanoscale* 2020; 12: 13055.
 Stehlik et al, *Carbon* 2021; 171: 230.

Steinerova et al, *Mater. Sci. Eng. C* 2021; 121:111792
 Bydžovská et al, *Nanomaterials* 2021; 11:2251
 Kratka et al, *Colloids Surf. B* 2021; 204:111689

Nemcakova et al, *Sci. Rep.* 2022; 12:5264
 Mortet et al, *Diam. Relat. Mater.* 2022; 124:108928
 S. Stehlik et al, *Diam. Relat. Mater.* 2023; 134: 109754

Budil et al, *Lett. Appl. Microbiol.* 2022; 74:924
 Budil et al, *Appl. Spectrosc.* 2023; 77:500
 ...work in progress...

New types of materials (M4.17)



Targeted manipulation, organized micro and nano-structures (M4.18)



Study of interaction with modified surfaces, cell culture studies (M4.19)



Concepts with osteogenic, epithelial and stem cell cultures (M4.20)



6/2023

Future Plans and Risks (Sustainability)

- ❑ Continue and expand cooperation within created cluster of RP4 and other partners



SLOVAKIA

Cells on Diamond

Dr. Katarína Kozics

New project from 2023



FHV
Vorarlberg University
of Applied Sciences

AUSTRIA

Microfluidics/lab-on-chip

Prof. Fadi Dohnal

Project starting in 7/2023

- ❑ Expanding international visibility and cooperation



ULSAN NATIONAL INSTITUTE OF
SCIENCE AND TECHNOLOGY

KOREA

Organic materials

Prof. Geunsik Lee

Project submitted in 5/2023



ORTOPEDICKÁ KLINIKA FAKULTY ZDRAVOTNICKÝCH STUDIÍ
UNIVERZITY J. E. PURKYNĚ V ÚSTÍ NAD LABEM A KRAJSKÉ ZDRAVOTNÍ, a. s.
– MASARYKOVY NEMOCNICE V ÚSTÍ NAD LABEM, o. z.

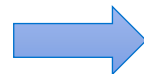
CZECHIA

Orthopedics/implants

MUDr. Tomáš Novotný

Project to be submitted in 6/2023

- ❑ Critical systematic review of current state of the art



UNIVERSITY OF
CHEMISTRY AND
TECHNOLOGY
PRAGUE

CZECHIA

Microbiology

Prof. Kateřina Demnerová

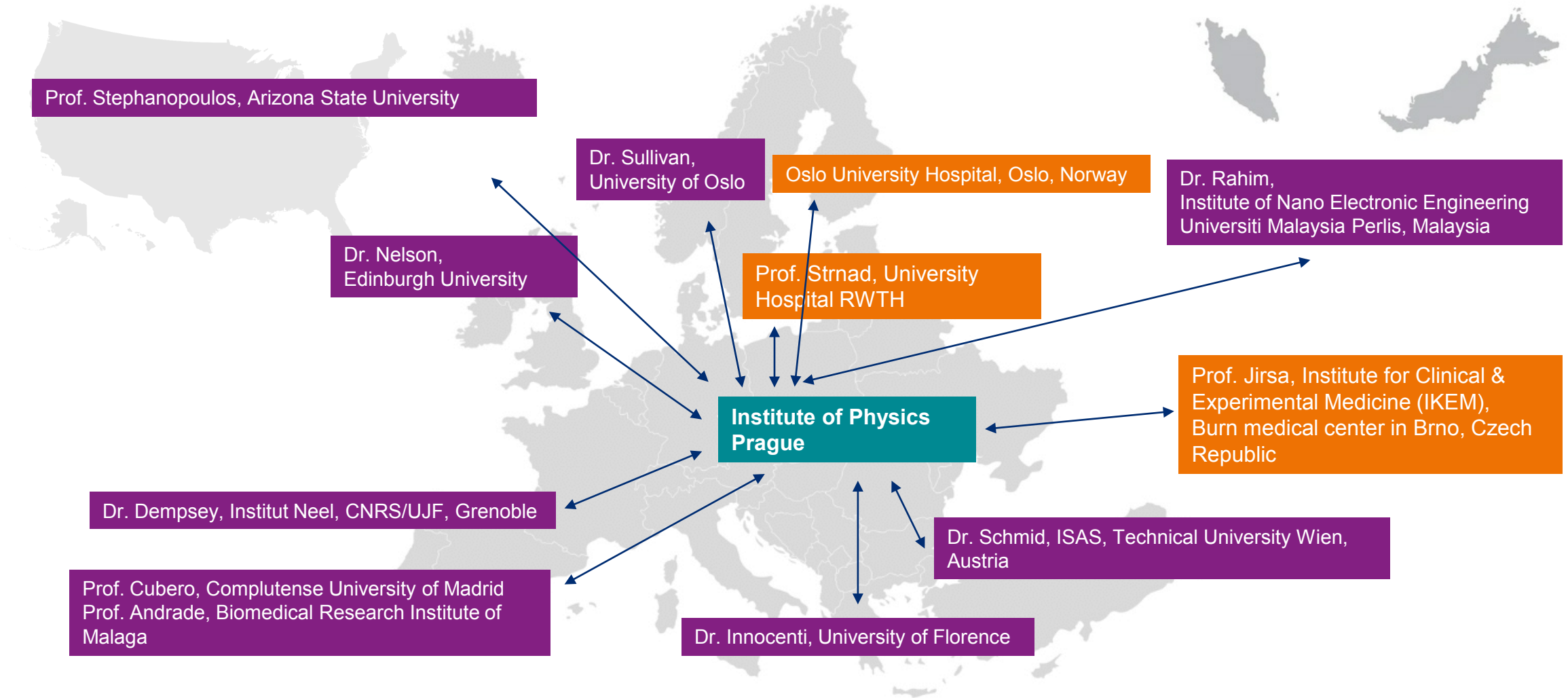
Project preparation
with the USA partner



FZU

Fyzikální ústav
Akademie věd
České republiky

Research Cooperation Network





Některé léky mohou poškozovat játra. Vědci vyvíjejí model orgánu ke sledování „4D“ mikroskopem

© 22. říjen 2021 | Věda Plus



Vědec, biolog, poznámky, telefon, rukavice, laboratoř, infekce, výzkum, koronavirus, ilustrační foto | Foto: Fotobanka Profimedia



K čemu má sloužit spolehlivý model jater? Odpovídá reportáž Martina Srba

Outreach Activities

NANOSTRUKTURY DNA JAKO NOVÉ NOSIČE PRO SUBCELULÁRNÍ CÍLENÍ

science 20. 10. 2021 Tiskové zprávy

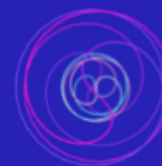
Při vystavení DNA nanostruktur biologickým kapalinám dojde k jejich pokrytí proteinovým obalem.

Cílené doručování léčiv je předmětem zájmu vědců z celého světa. K této problematice nyní výrazně přispěli i vědci z Laboratoře biofyziky pod vedením Olega Lunova. Ti se zabývali biologickými vlastnostmi a účinností transportu látek do buněk s pomocí DNA nanostruktur (DN).

DOPORUČUJEME



Česká republika bude



Young Investigators
Seminar Series

3RD WEDNESDAY OF EACH
MONTH @16.30 PM (CEST)

Long-term Sustainability and Top-quality Research



Interdisciplinary platform

gain deep insights in **fundamental mechanistic understanding** of how selected physical factors

ISAB critics and comments

Prof Raul J. ANDRADE Biomedical Research Institute of Malaga Spain

Prof M.Isabel LUCENA University of Málaga, Spain



Fyzikální ústav
Akademie věd
České republiky

Prof Guruprasad AITHAL
Nottingham Digestive Diseases Centre UK

Boosting international visibility

With Prof. Job Dekker (University of Massachusetts Medical School) applied for The Human Frontier Science Program

Collaborations with teams having deep knowledge in drug/treatment

Developing novel research directions

Liver organoids; DNA nanostructures as novel bionanomaterial;

Involvement of students and young researchers



Centrum Radius
Na dosah vědomostí

Visiting PhD students for internship or Short-Term Scientific Missions

Conditions for commercialisation of research results



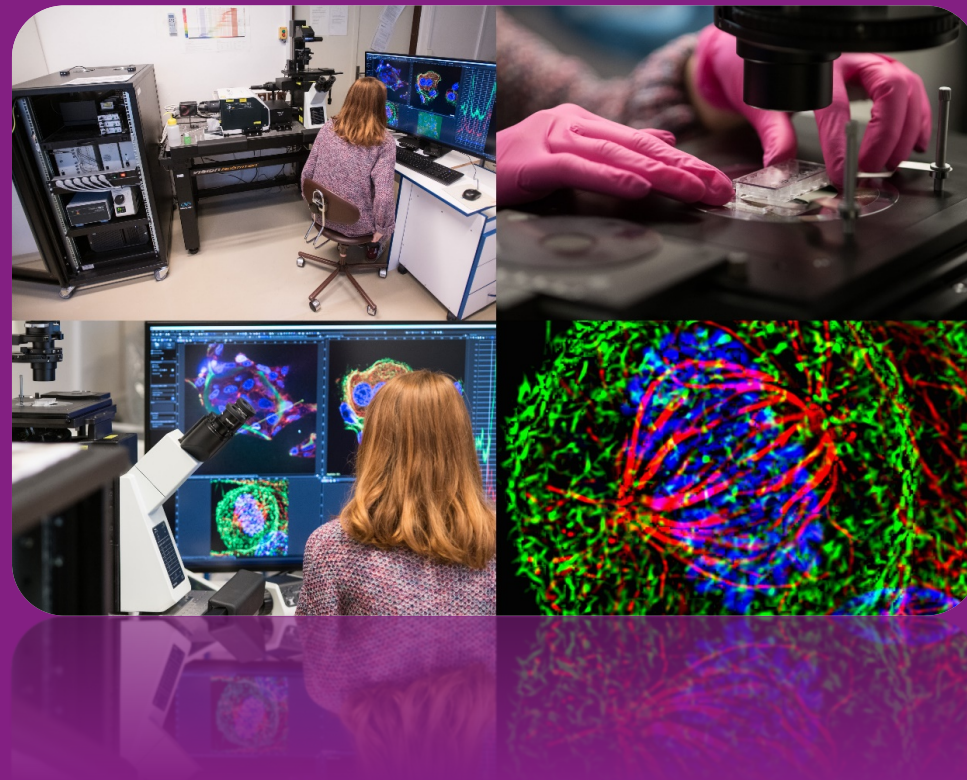
Thank you!

Research program 4 – “Physics for Bio”

cutting-edge physical research directed at biology and medicine



The project Solid state physics for the 21st century – SOLID21
CZ.02.1.01/0.0/0.0/16_019/0000760 is co-funded by the European Union.



EVROPSKÁ UNIE
Evropské strukturální a investiční fondy
Operační program Výzkum, vývoj a vzdělávání

