Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

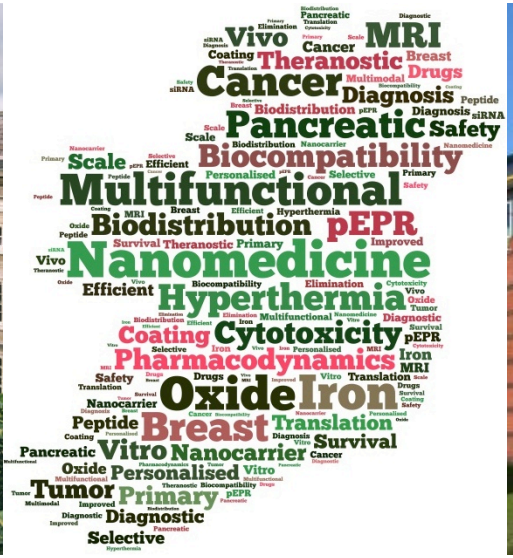
Nanomedicine for drug delivery in cancer therapy

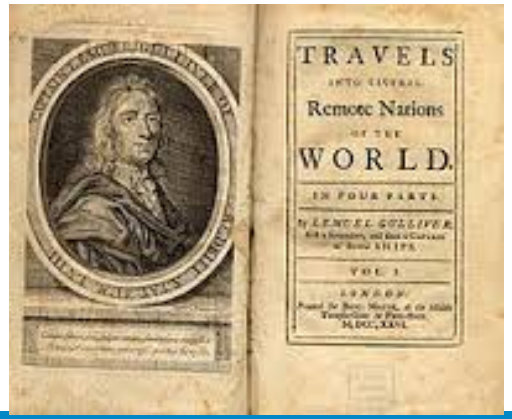
Adriele Prina-Mello, MSc, PhD

School of Medicine, AMBER centre, CRANN Institute, Trinity College Dublin
&
European Technology Platform in Nanomedicine

NUOVE FRONTIERE NELLA TERAPIA DELLE MALATTIE ONCOLOGICHE ED ONCOEMATOLOGICHE
Treviso, 20 Novembre 2015, Sala Congressi, Ospedale Ca' Foncello

Trinity College Dublin, Ireland





TCD: European Technology Platform in Nanomedicine: Annual Event bringing the community together

Attracted 120 Nanomedicine key players for 3 days at the Trinity Translational Medicine Institute
First Translational Projects to go forward for Industrial support and funding

Featured in this month Nature Nanotechnology 2015

TCD: EURONANOFORUM 2015 – FUTURE FLASH! BEST PROJECT

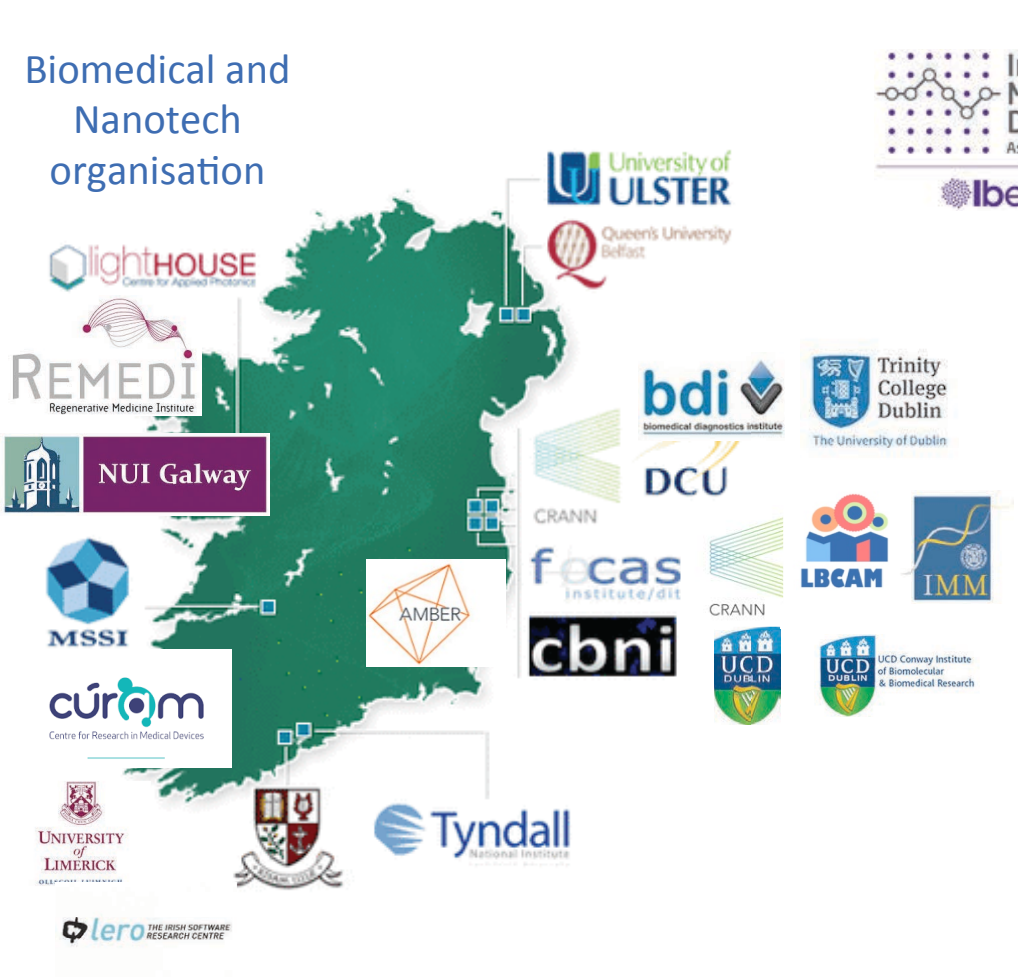
NAMDIATREAM

NANOTECHNOLOGICAL TOOLKITS
FOR MULTI-MODAL DISEASE DIAGNOSTICS
AND TREATMENT MONITORING

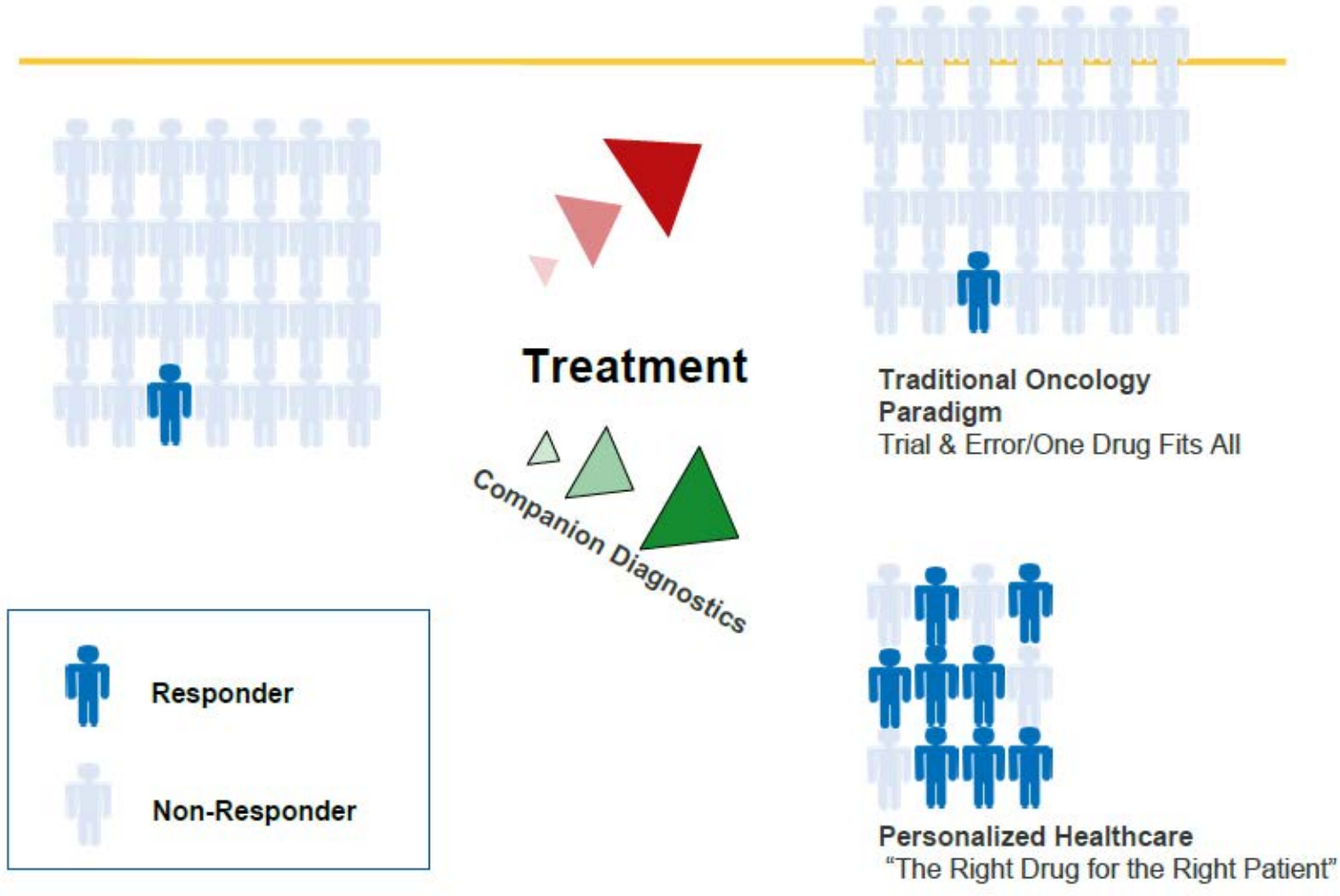
NAMDIATREAM awarded as
the best NMP European project
out of more than 1000
EU funded projects
at EuroNanoForum 2015
(Riga, Latvia, June 2015)

The Irish Biomedical Landscape

Biomedical and Nanotech organisation

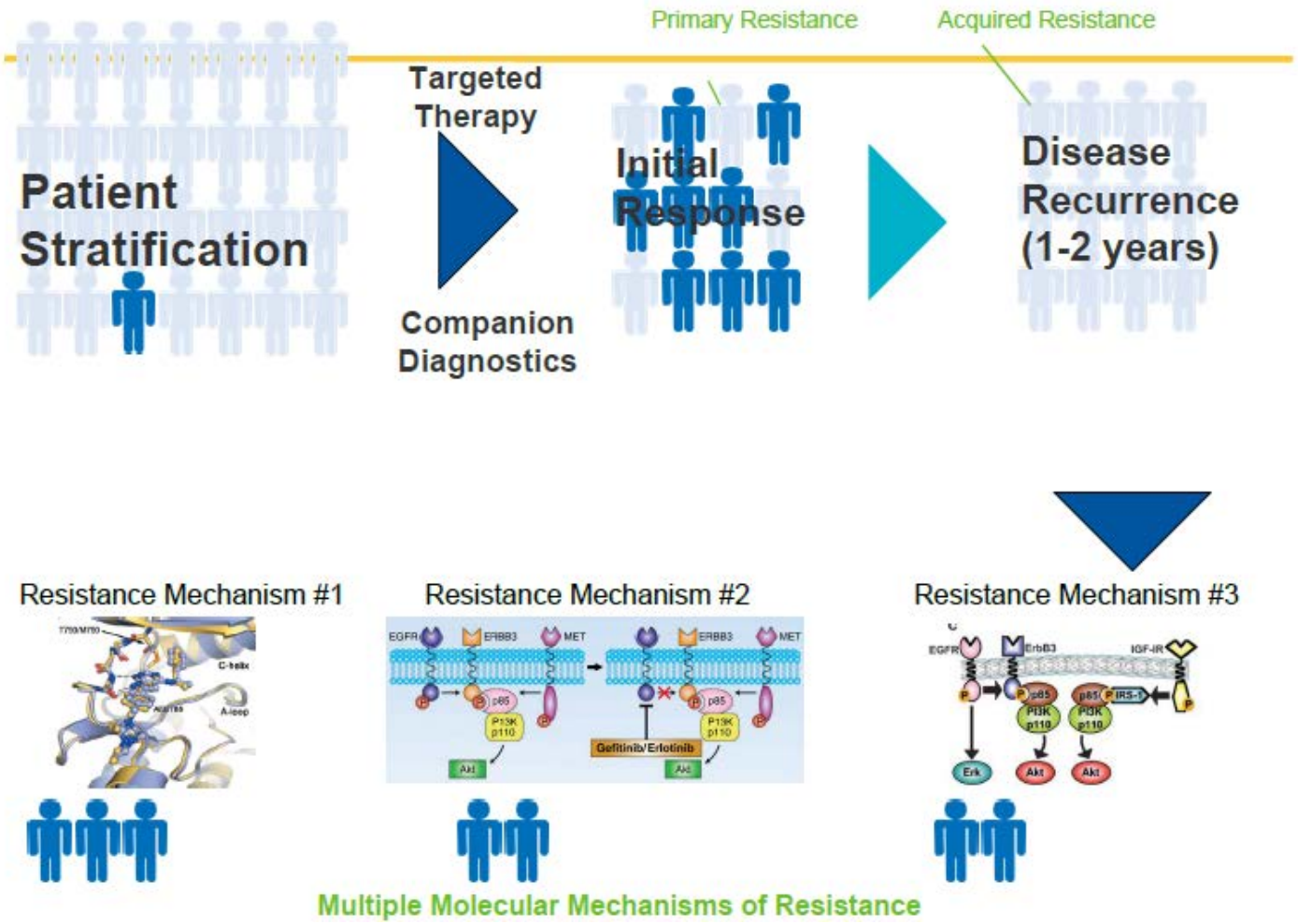


Personalised medicine: companion diagnostics model: useful but simplified



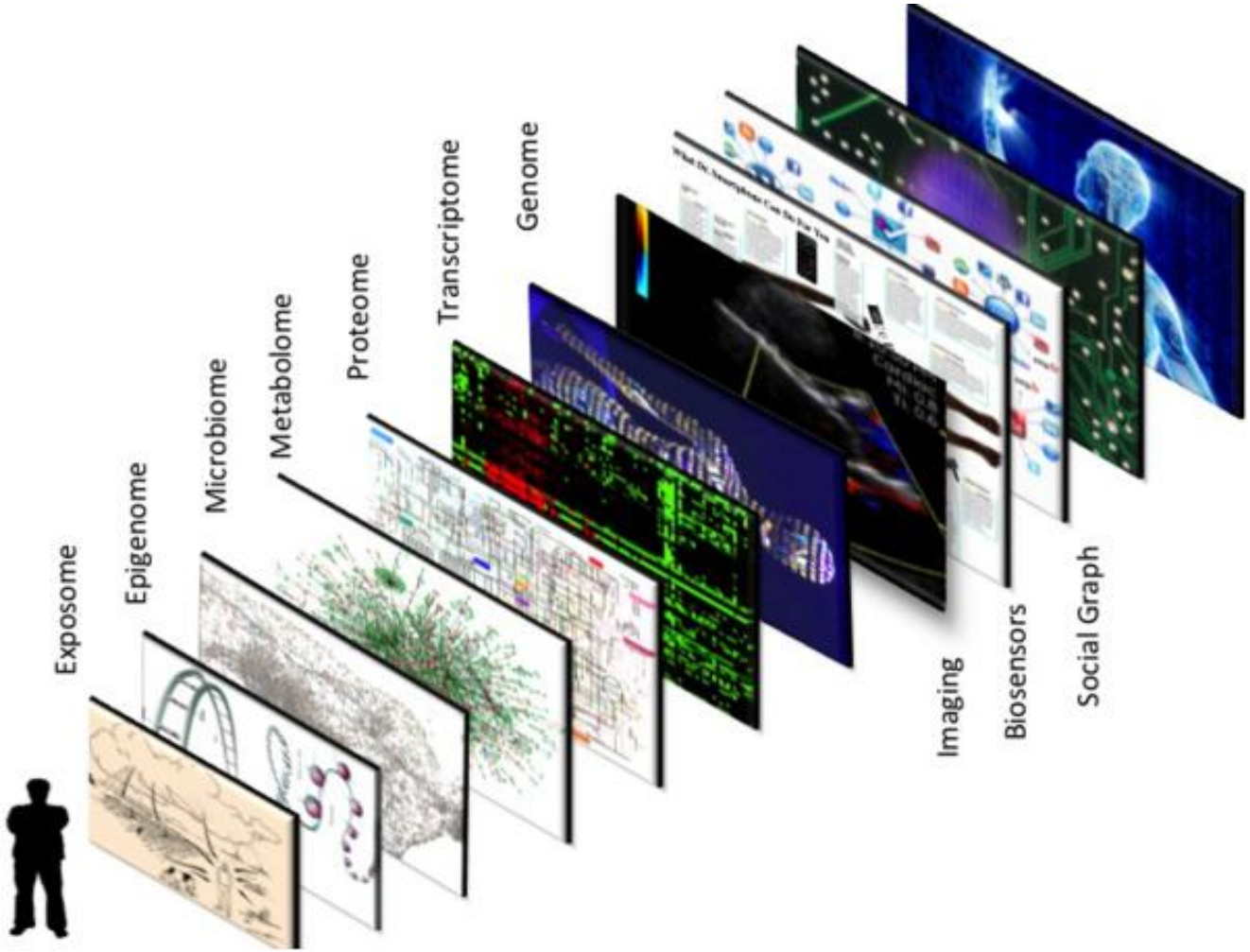
Courtesy of Prof. J. O'Leary, Head of Histopathology, St. James's Hospital, Ireland

Personalised health care: the emerging reality



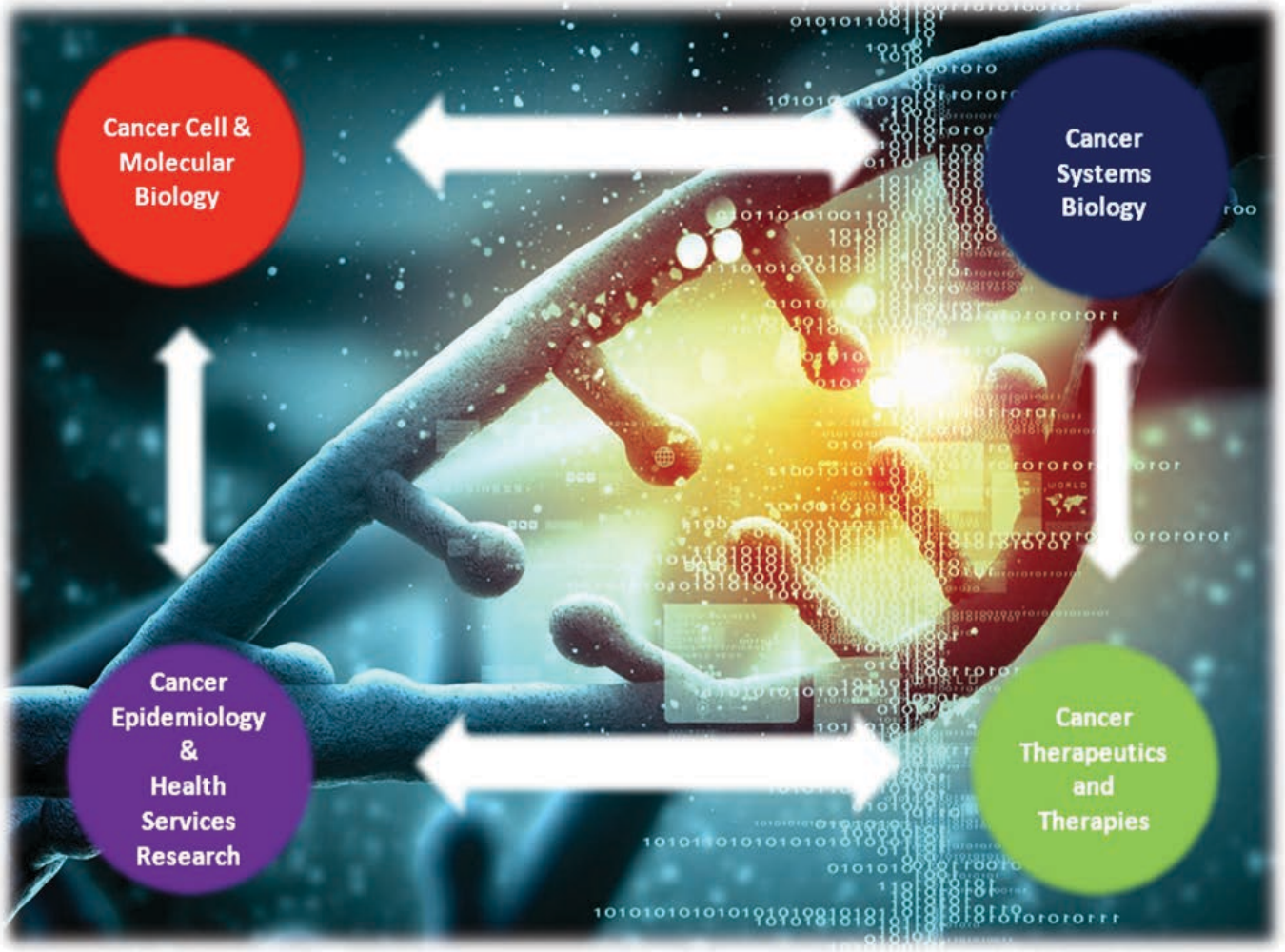
Courtesy of Prof. O'Leary

How far can we go towards precision medicine?



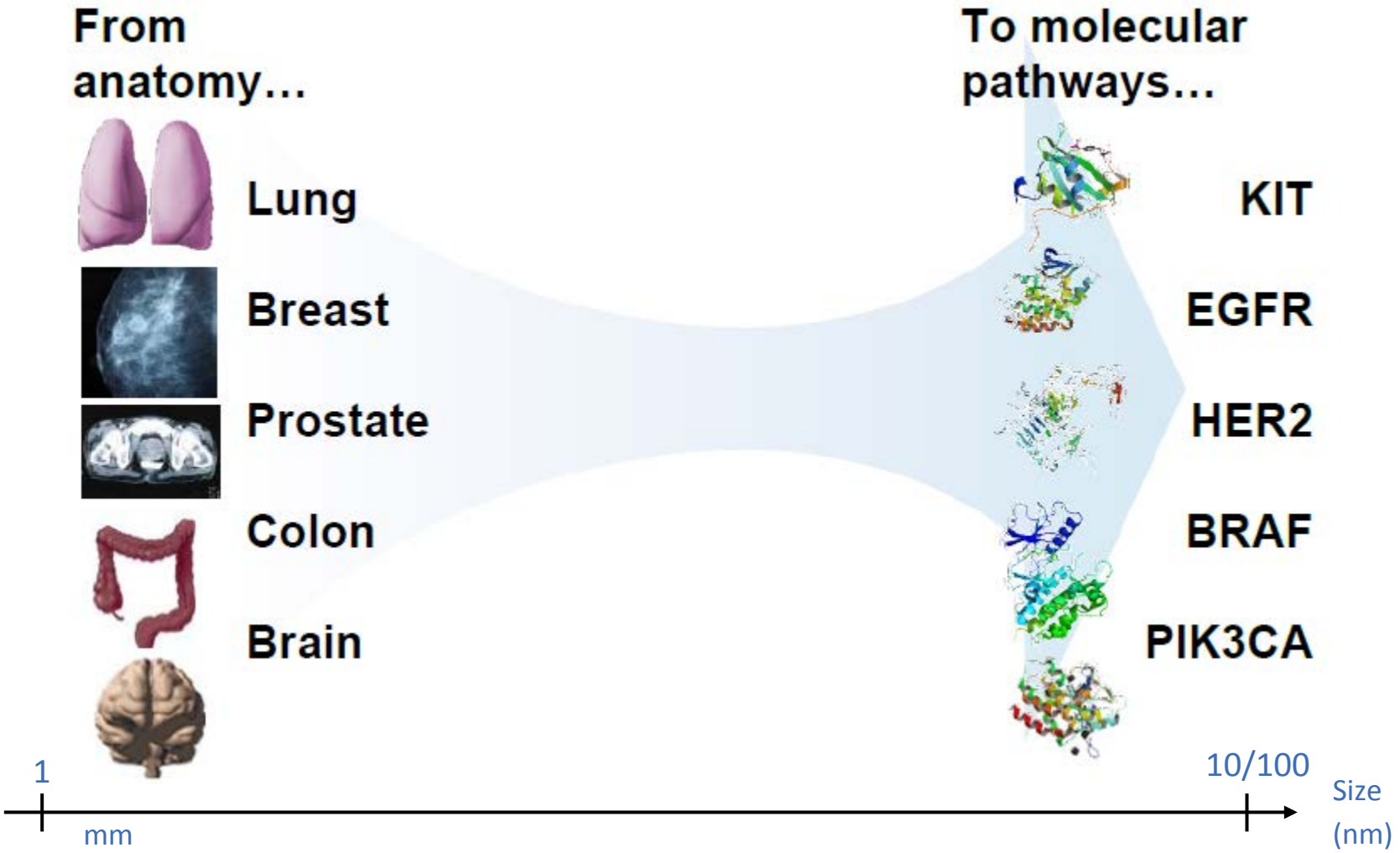
Courtesy of Prof. O'Leary

Cancer at TCD and integrated areas



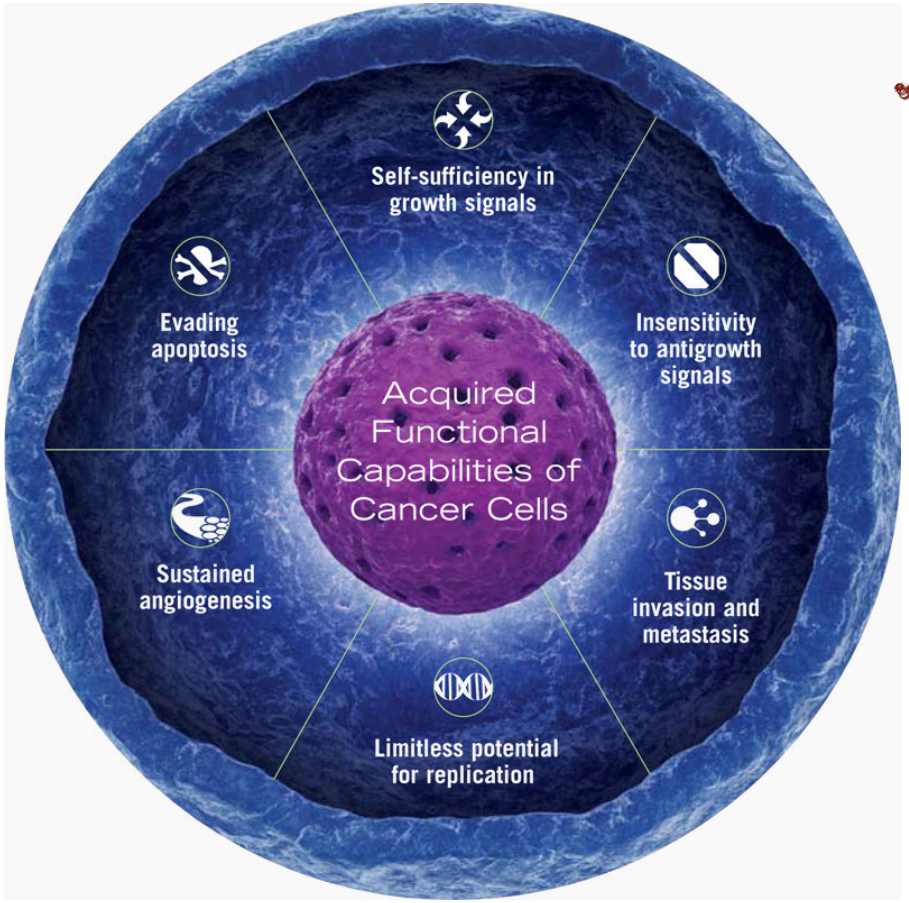
Courtesy of Prof. O'Leary

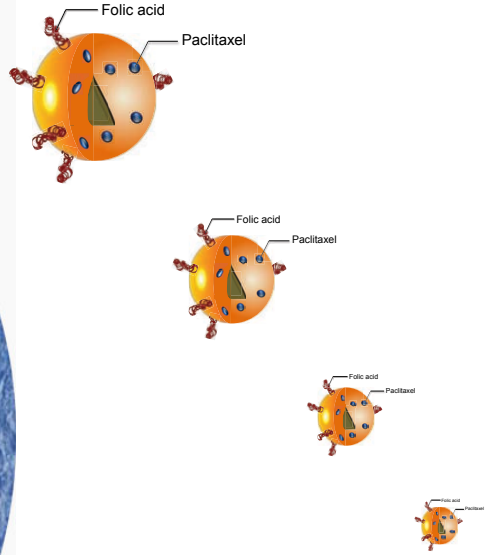
The changing view of Cancer



Courtesy of Prof. O'Leary

It's the Cancer cell after all





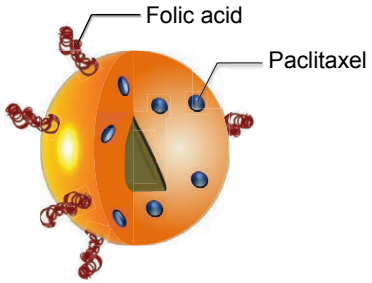
1 mm

10/100 Size (nm)

Courtesy of Prof. O'Leary

WHY NANOTECHNOLOGY in ONCOLOGY?

- New Diagnostics
- More Efficient drugs
- New Therapeutics
- New Combination Therapy
- Personalised Therapies



Solving unmet clinical needs

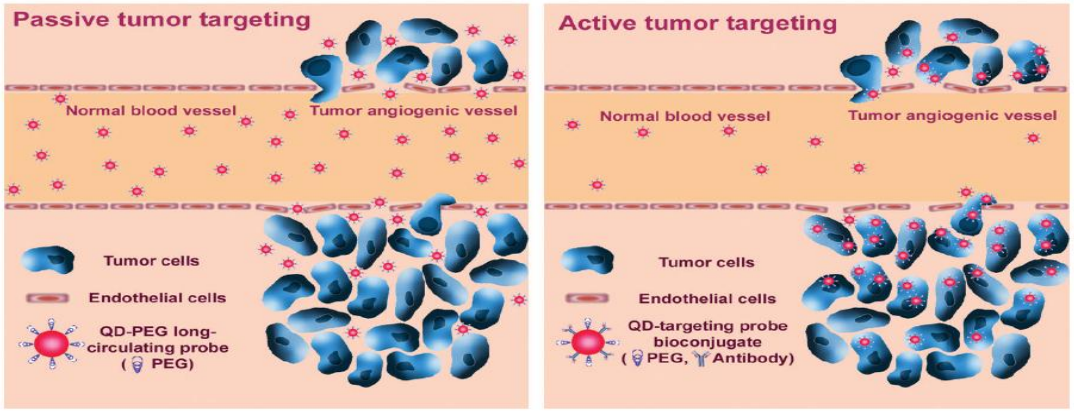
- Promising nanocarriers for delivery of imaging and therapeutic agents
- Can potentially improve the kinetics and dynamics of drug or metabolic delivery
- The **complexity of in vivo** systems imposes multiple **barriers** that severely inhibit efficiency and have to be overcome to fully exploit the theoretical potential of nanoparticles.

“NANO” - Benefits for Clinical Treatment

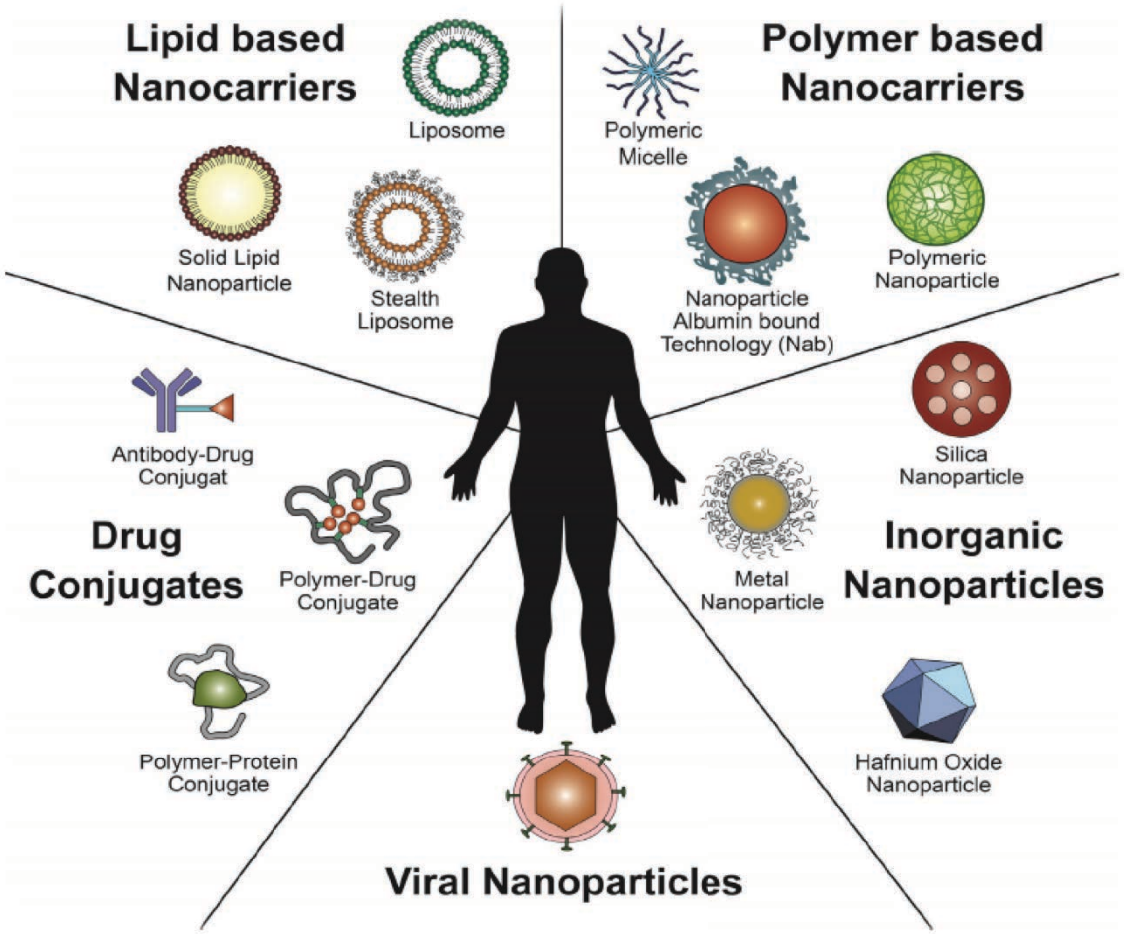
Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three methods risk damage to normal tissues or incomplete eradication of the cancer.

Nanotechnology offers the means to aim therapies directly and selectively at cancerous cells.

- Passive Targeting
- Active Targeting
- Nanocarriers (next slides)
- Destruction from Within (next slides)



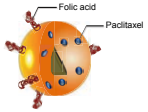
Nanocarriers for drug delivery and targeting

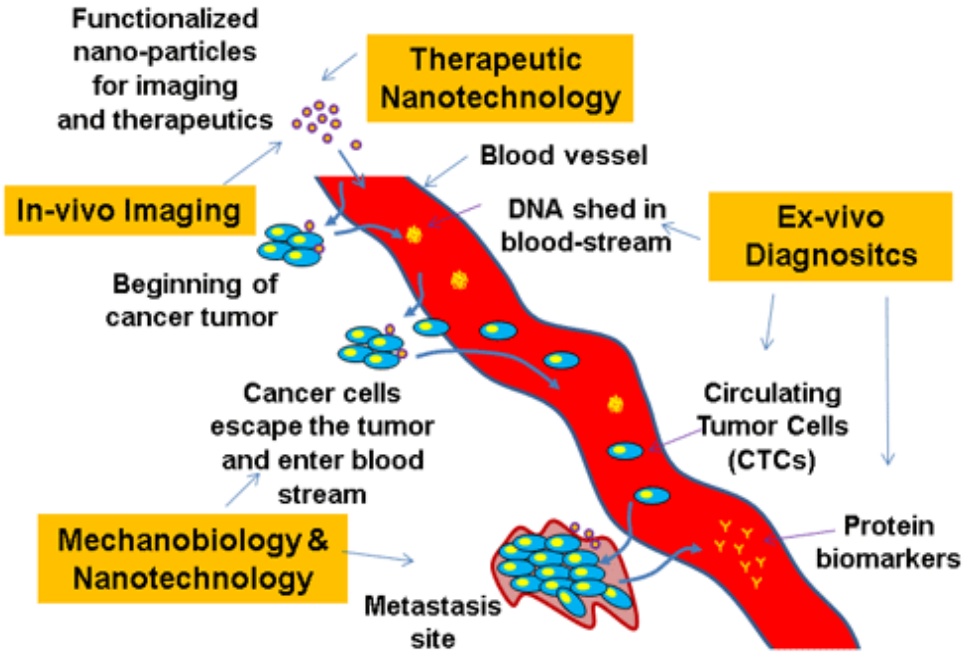


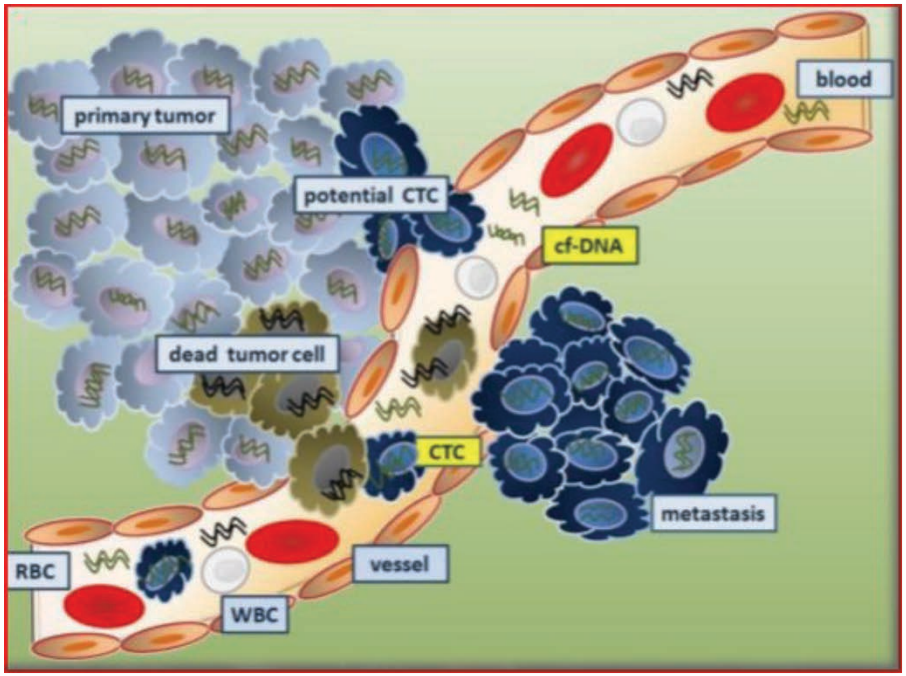
A whole range of delivery agents are possible but the main components typically include a nanocarrier, a targeting moiety conjugated to the nanocarrier, and a cargo (such as the desired chemotherapeutic drugs).

Source: Wicki WD et al 2015 Nanomedicine

Destruction from within

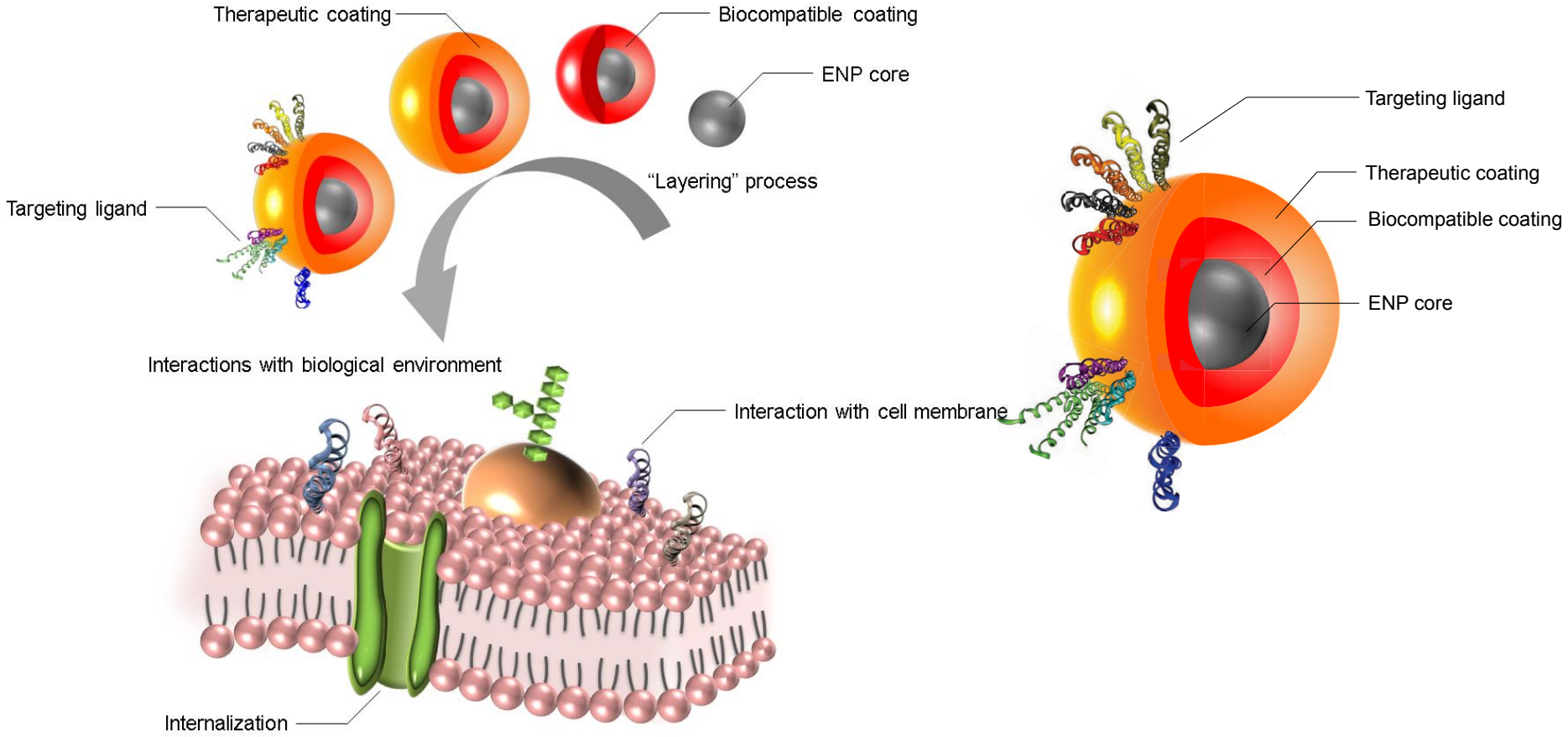






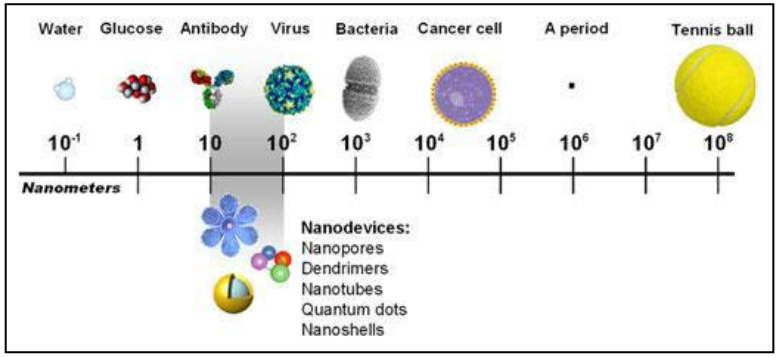
http://nano.cancer.gov and Nature Cancer review

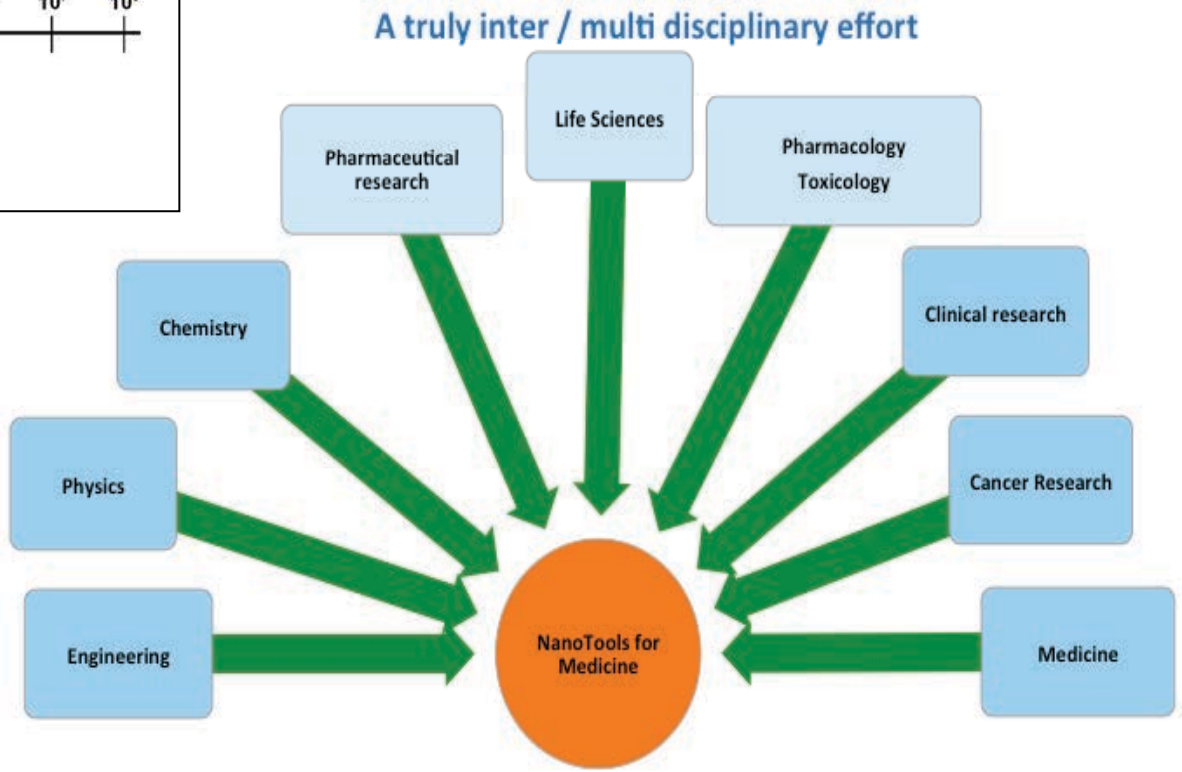
Nano-toolkit for effective targeting: Multilayered Nanotechnology



Book chapter: Movia D., C. Poland, L. Tran, Y. Volkov, A. Prina-Mello, Multilayered nanoparticles for personalized medicine: translation into clinical markets: 09/2013; ISBN: 9789814316170 In book: Handbook of Clinical Nanomedicine: From Bench to Bedside, Publisher: Pan Stanford Publishing, 2013

NANOMEDICINE: a multidisciplinary science





Source: Bregoli L., Gavin-Imedio J., Movia D., Prina-Mello A., 2015 Nanomedicine (Elsevier)

Nanomedicine products

Product name (year of clinical approval)	Supplier	Core nanomaterial	Administration route	Mode of action	Indication	Main advantage
Marqibo (2012)	Talon Therapeutics Inc.	Liposome	I.V.	Drug delivery (drug: vincristine)	Philadelphia chromosome negative ALL	Reduced side effects vs. free drug
NanoTherm (2010)	MagForce Nanotech AG	Iron-oxide NP	Stereotactic	Magnetic thermotherapy [13]	Glioblastoma	Increased overall survival vs. standard treatment
Genexol/ Cynviloq (2007)	Samyang Biopharma. (South Korea)	Micelle	I.V.	Drug delivery (drug: paclitaxel)	NSCLC and metastatic breast cancer	Reduced side effects vs. free drug
Rexin-G (2007)	Epeius Biotechnologies Corp. (Philippines)	Pathotropic NP	I.V.	miR122 targeting [24]	All metastatic solid malignancies	Increased survival vs. chemotherapy alone
Abraxane (2005)	Abraxis Bioscience/ Celgene Europe	Albumin-bound NP	I.V.	Drug delivery [11] (drug: paclitaxel)	Metastatic lung and breast cancer	Reduced side effects vs. free drug
Myocet (2000)	Sopherion Therapeutics, LLC and Cephalon, Inc.	Non-PEGylated liposome	I.V.	Drug delivery (drug: doxorubicin)	Metastatic ovarian and breast cancers, HIV-Kaposi sarcoma	Reduced side effects vs. free drug
Ontak (1999)	Seragen, Inc.	Fusion protein	I.V.	Drug delivery (drug: Diphtheria toxin)	Cutaneous T-cell lymphoma	Reduced risk of tumour progression
DaunoXome (1996)	Galen, Ltd.	Non-PEGylated liposome	I.V.	Daunorubicine citrate delivery	Advanced HIV-Kaposi sarcoma	Reduced side effects vs. standard chemotherapy alone
Doxil (1995)	Centocor Ortho Biotech, J&J	PEGylated liposome	I.M.	Drug delivery (drug: doxorubicin) [12]	Metastatic ovarian and breast cancers, HIV-Kaposi sarcoma and multiple myeloma	Reduced side effects vs. free drug
Oncaspar (1994)	Enzon Pharmaceutical, Inc.	Polymeric NP	I.V./I.M.	Drug delivery (drug: L-asparginase)	ALL	Reduced side effects vs. free L-asparginase

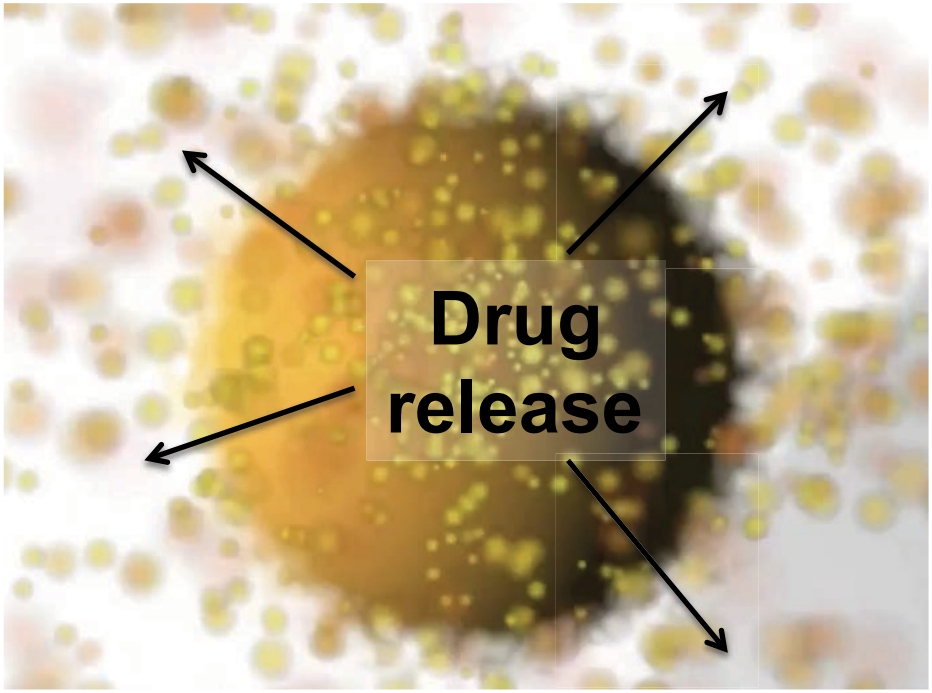
Bregoli et al, 2015, Nanomedicine (Elsevier)

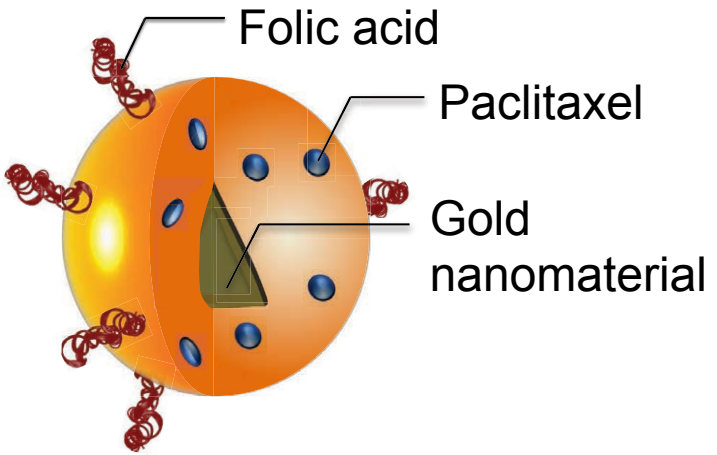
Nanomedicine approved products

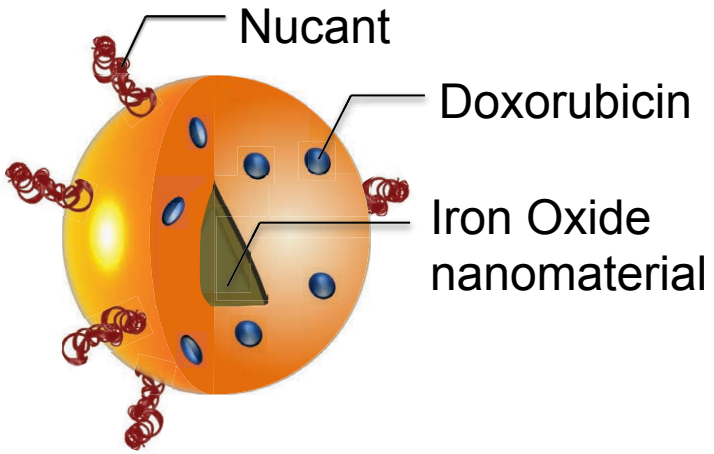
Product name (year of clinical approval)	Supplier	Core nanomaterial	Administration route	Mode of action	Indication	Main advantage
Marqibo (2012)	Talon Therapeutics Inc.	Liposome	I.V.	Drug delivery (drug: vincristine)	Philadelphia chromosome negative ALL	Reduced side effects vs. free drug
NanoTherm (2010)	MagForce Nanotech AG	Iron-oxide NP	Stereotactic	Magnetic thermotherapy [13]	Glioblastoma	Increased overall survival vs. standard treatment
Genexol/ Cynviloq (2007)	Samyang Biopharma. (South Korea)	Micelle	I.V.	Drug delivery (drug: paclitaxel)	NSCLC and metastatic breast cancer	Reduced side effects vs. free drug
Rexin-G (2007)	Epeius Biotechnologies Corp. (Philippines)	Pathotropic NP	I.V.	miR122 targeting [24]	All metastatic solid malignancies	Increased survival vs. chemotherapy alone
Abraxane (2005)	Abraxis Bioscience/ Celgene Europe	Albumin-bound NP	I.V.	Drug delivery [11] (drug: paclitaxel)	Metastatic lung and breast cancer	Reduced side effects vs. free drug
Myocet (2000)	Sopherion Therapeutics, LLC and Cephalon, Inc.	Non-PEGylated liposome	I.V.	Drug delivery (drug: doxorubicin)	Metastatic ovarian and breast cancers, HIV-Kaposi sarcoma	Reduced side effects vs. free drug
Ontak (1999)	Seragen, Inc.	Fusion protein	I.V.	Drug delivery (drug: Diphtheria toxin)	Cutaneous T-cell lymphoma	Reduced risk of tumour progression
DaunoXome (1996)	Galen, Ltd.	Non-PEGylated liposome	I.V.	Daunorubicine citrate delivery	Advanced HIV-Kaposi sarcoma	Reduced side effects vs. standard chemotherapy alone
Doxil (1995)	Centocor Ortho Biotech, J&J	PEGylated liposome	I.M.	Drug delivery (drug: doxorubicin) [12]	Metastatic ovarian and breast cancers, HIV-Kaposi sarcoma and multiple myeloma	Reduced side effects vs. free drug
Oncaspar (1994)	Enzon Pharmaceutical, Inc.	Polymeric NP	I.V./I.M.	Drug delivery (drug: L-asparginase)	ALL	Reduced side effects vs. free L-asparginase

Bregoli et al, 2015, Nanomedicine (Elsevier)

“Nano-toolkit”

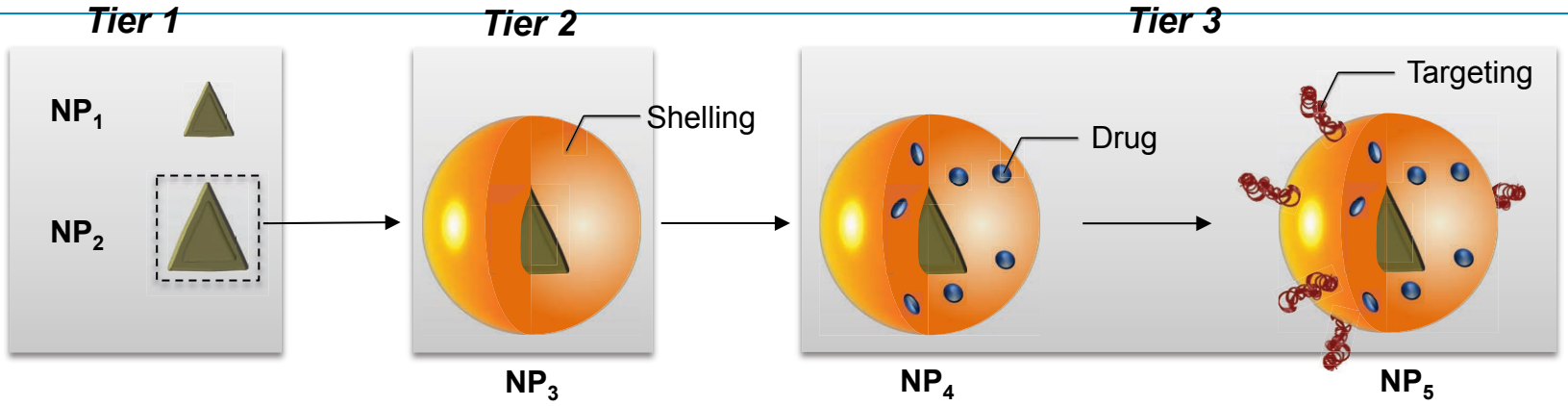


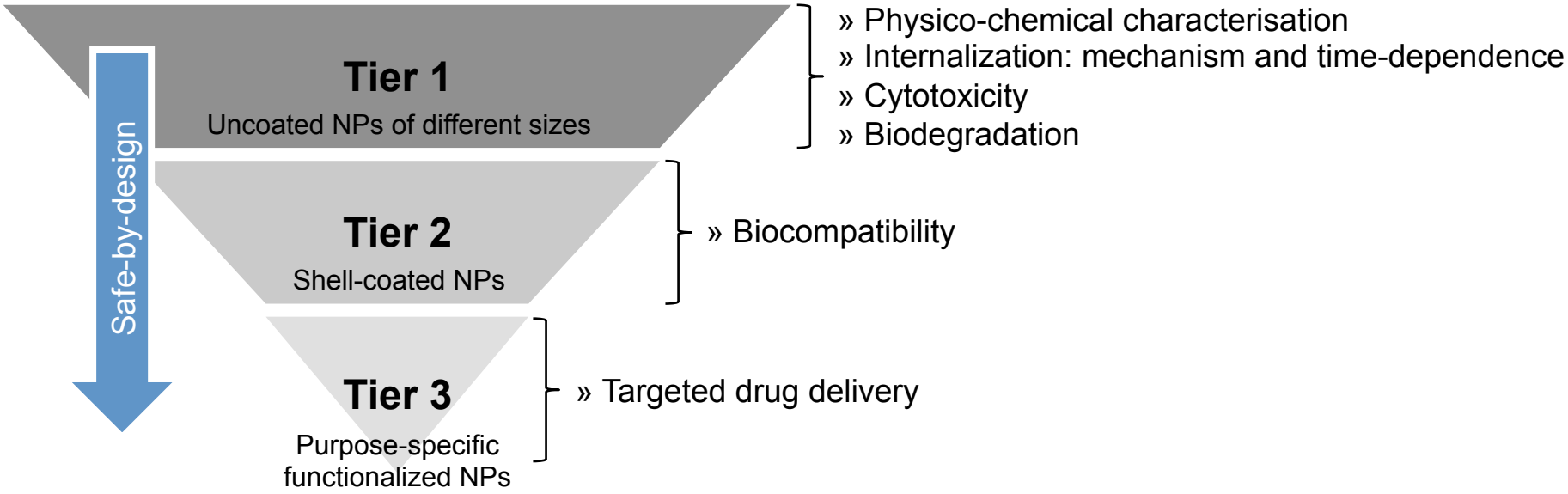




Movia D. *et al.,* Biomaterials, 2014, Prina-Mello et al., IEEE Trans Mag 2012

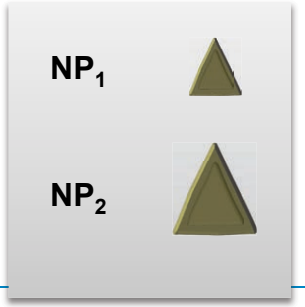
Engineering Nanomedicine: Safe by design approach



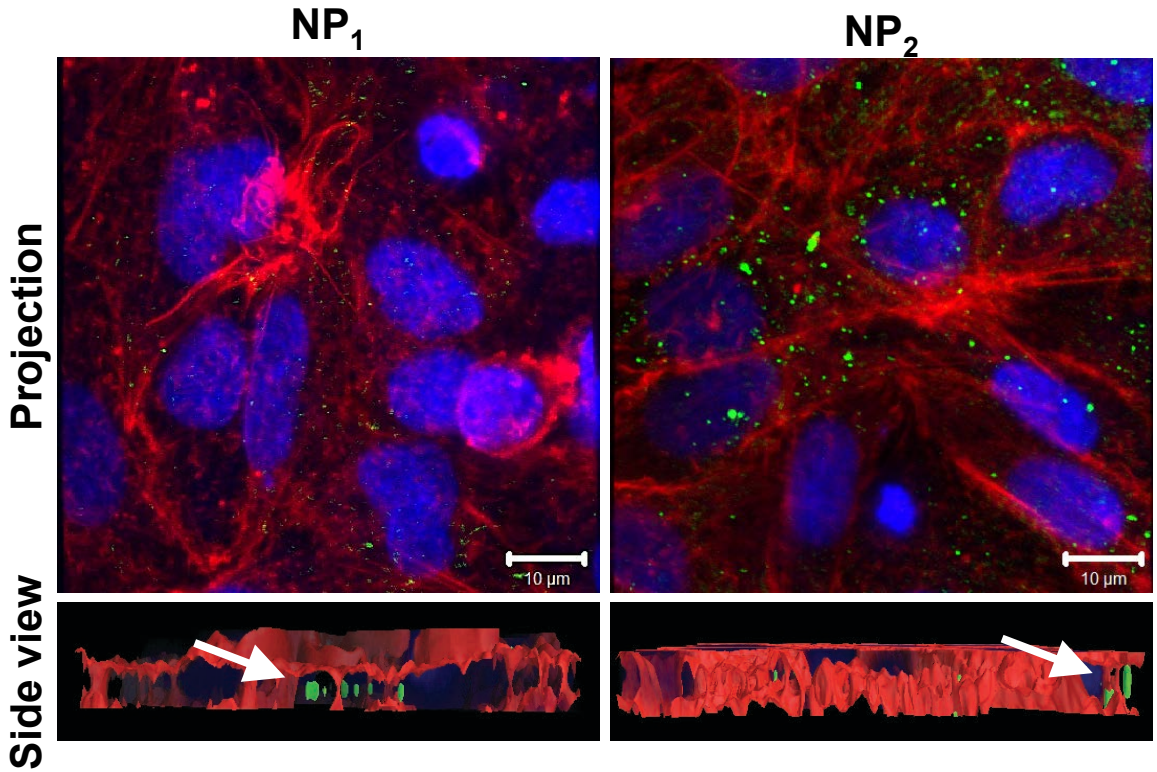


Source: Movia D. *et al.*, Biomaterials, 2014, 35, 9, 2543-2557 (selected by the editor as leading opinion paper)

“Safe-by-Design” – Tier 1

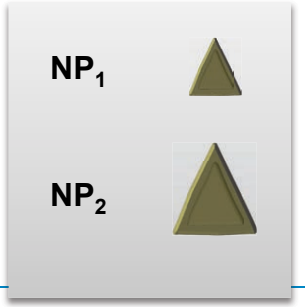


→ Cellular internalization

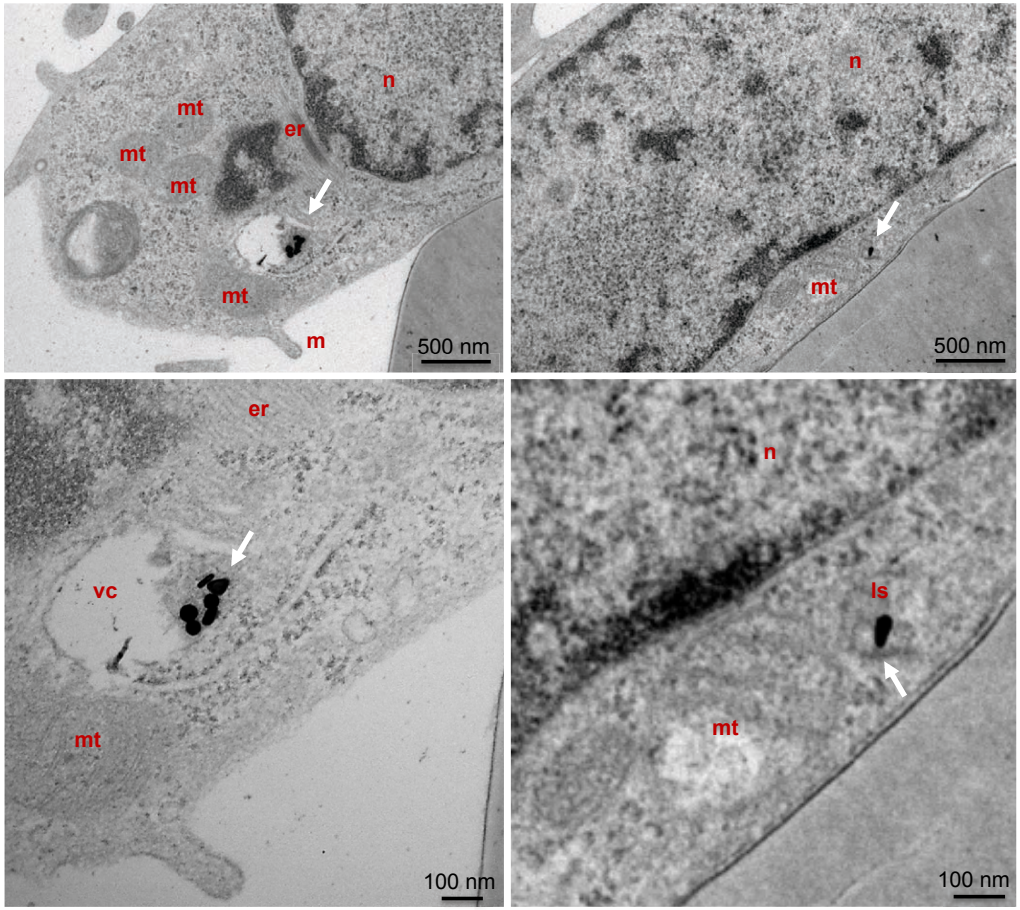


Adapted from Movia D. *et al.,* Biomaterials, 2014, 35, 9, 2543-2557

“Safe-by-Design” – Tier 1

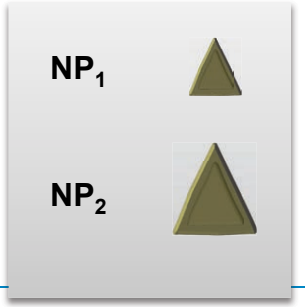


→ Cellular internalization

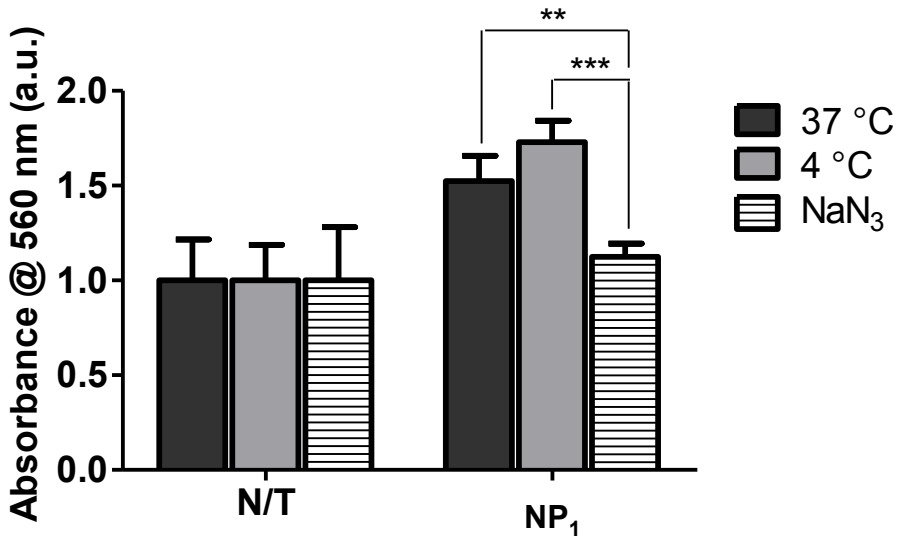


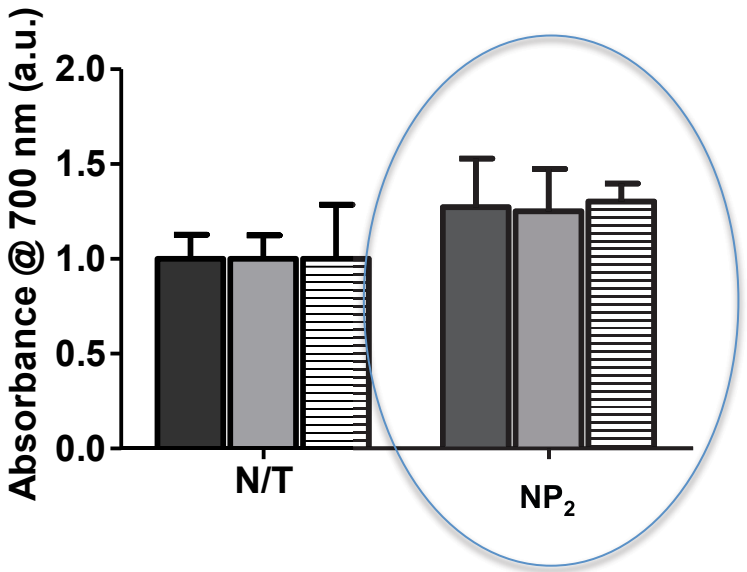
Adapted from Movia D. *et al.*, Biomaterials, 2014, 35, 9, 2543-2557

“Safe-by-Design” – Tier 1



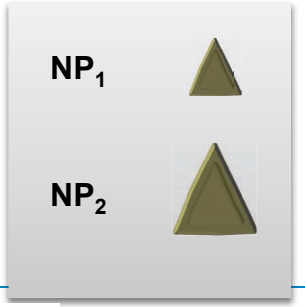
→ Cellular internalization



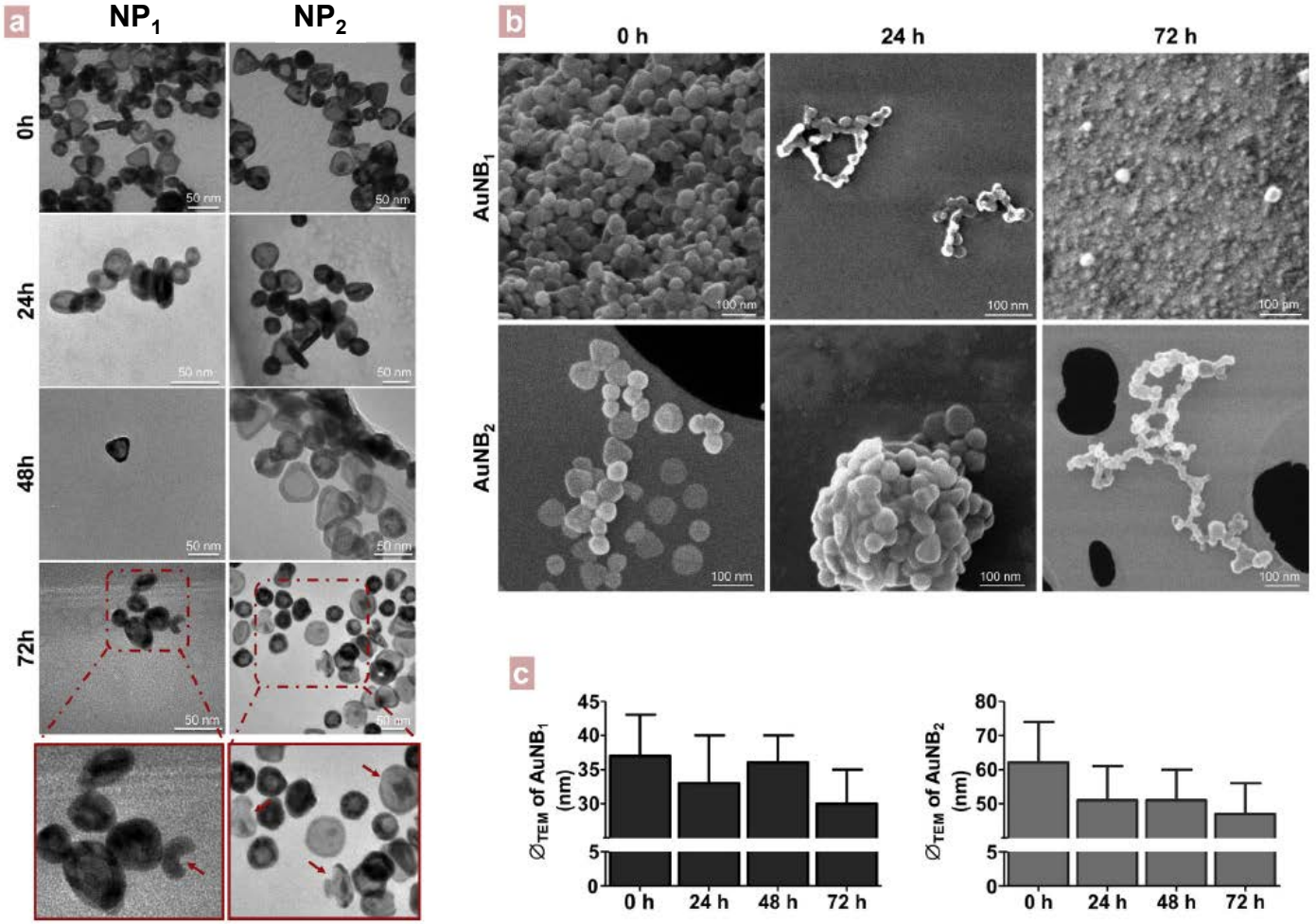


Adapted from Movia D. *et al.,* Biomaterials, 2014, 35, 9, 2543-2557

“Safe-by-Design” – Tier 1

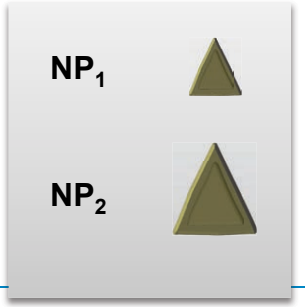


→ Biodegradation:

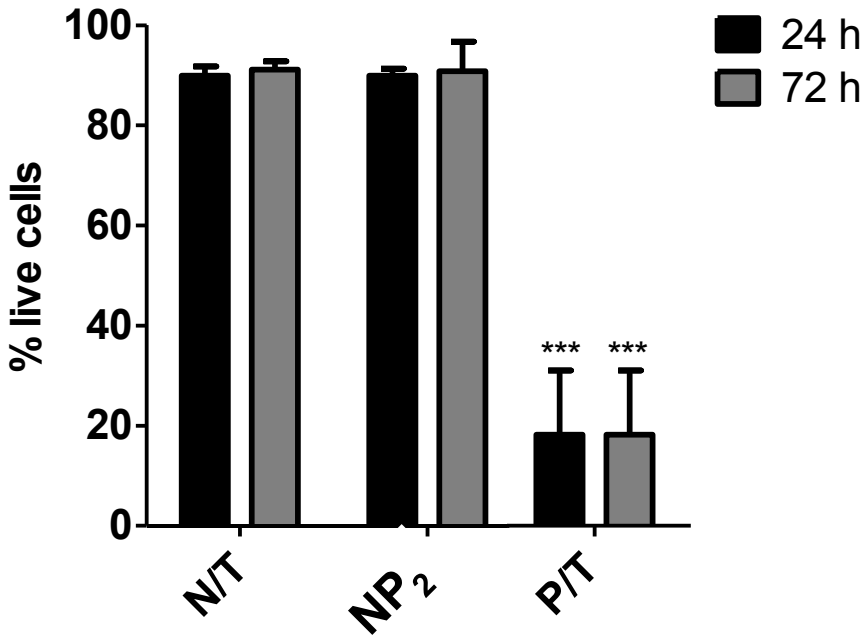


Adapted from Movia D. *et al.*, Biomaterials, 2014, 35, 9, 2543-2557

“Safe-by-Design” – Tier 1

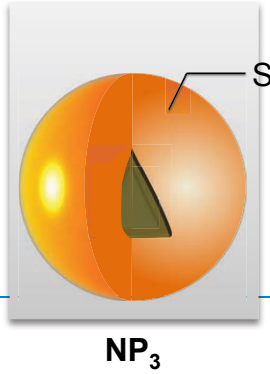


→ Cytotoxicity:

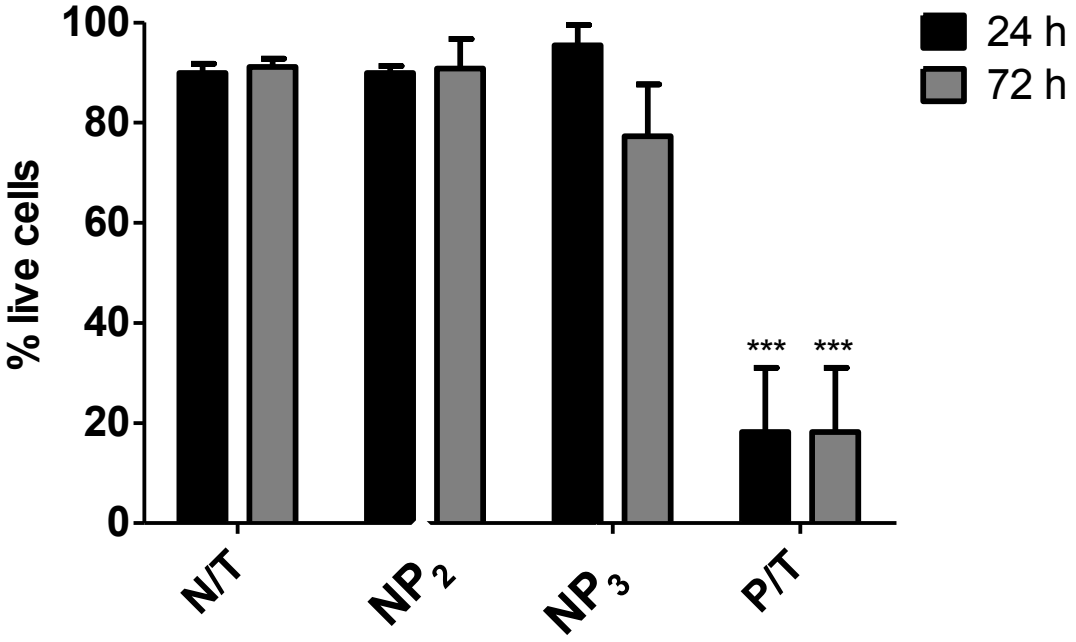


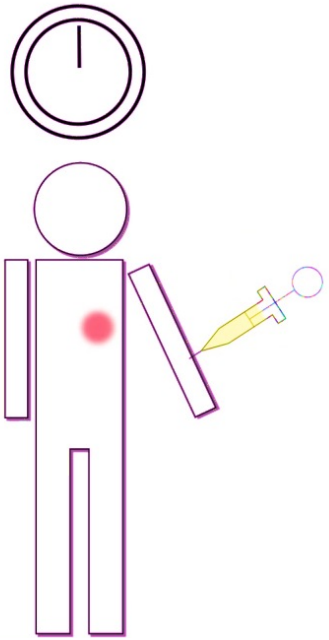
Adapted from Movia D. *et al.,* Biomaterials, 2014, 35, 9, 2543-2557

“Safe-by-Design” - Tier 2



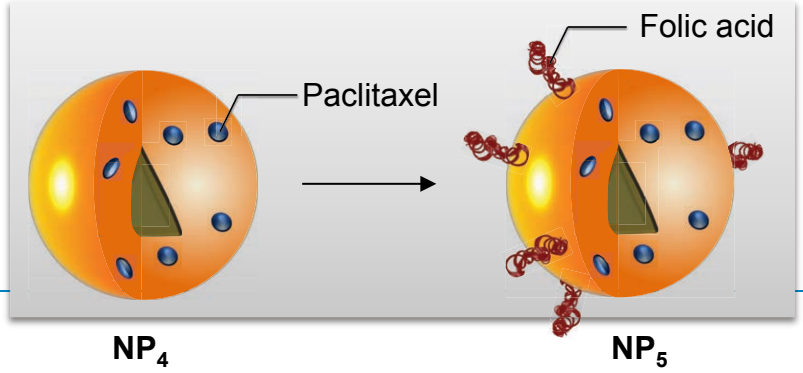
→ Biocompatibility:



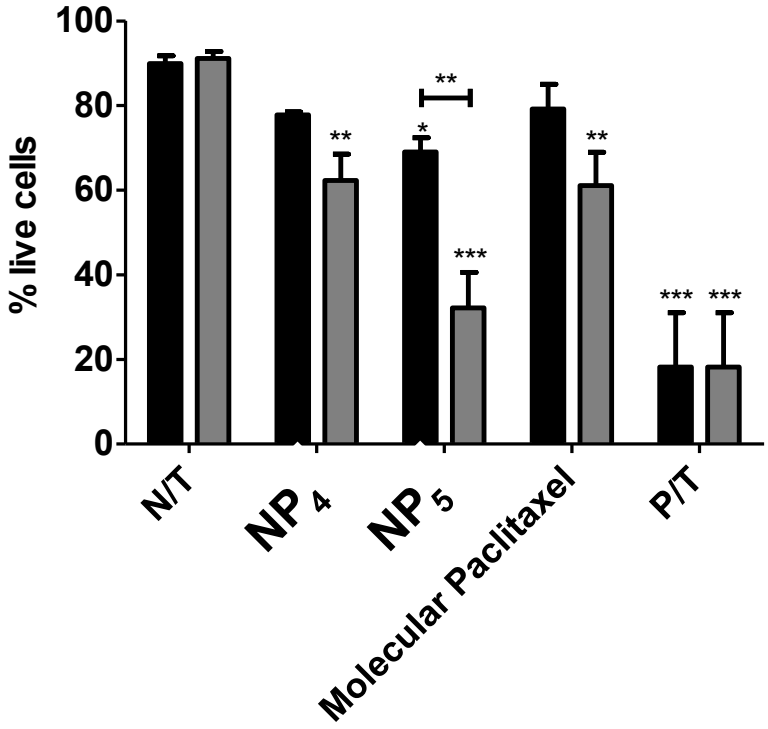


Adapted from Movia D. *et al.*, Biomaterials, 2014, 35, 9, 2543-2557

“Safe-by-Design” – Tier 3



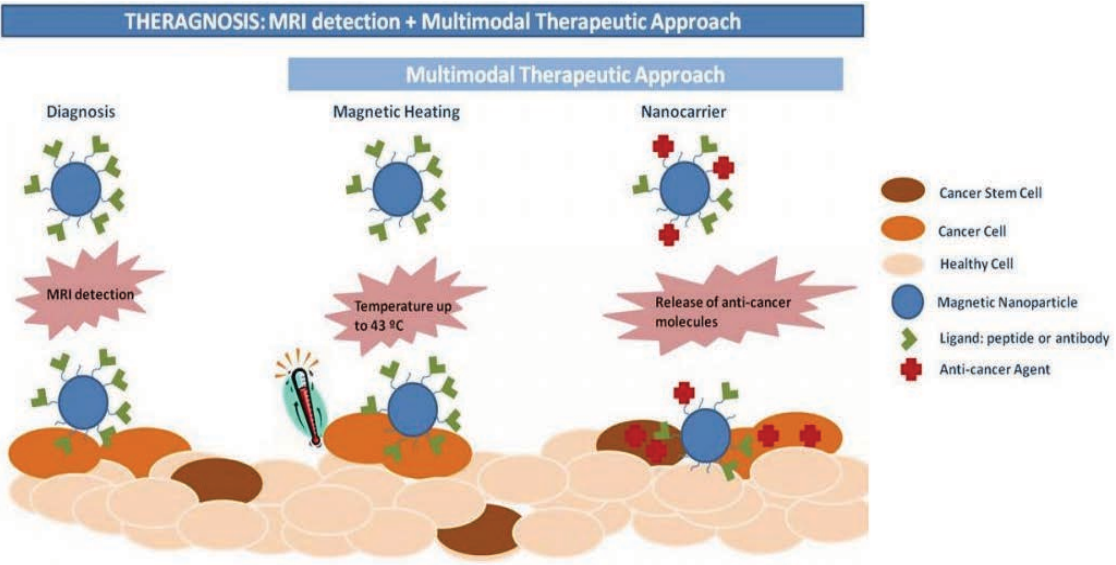
→ Targeted drug delivery:

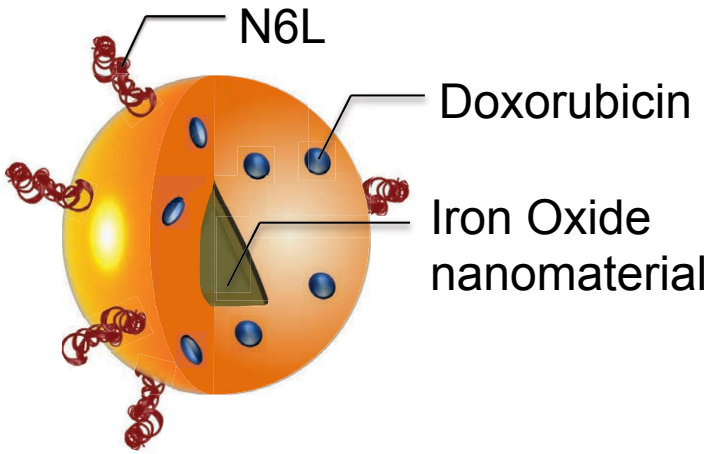


OUTCOME: Engineering Nanomedicines with SbD approach resulted in a safer and more effective drug delivery for lung cancer treatment

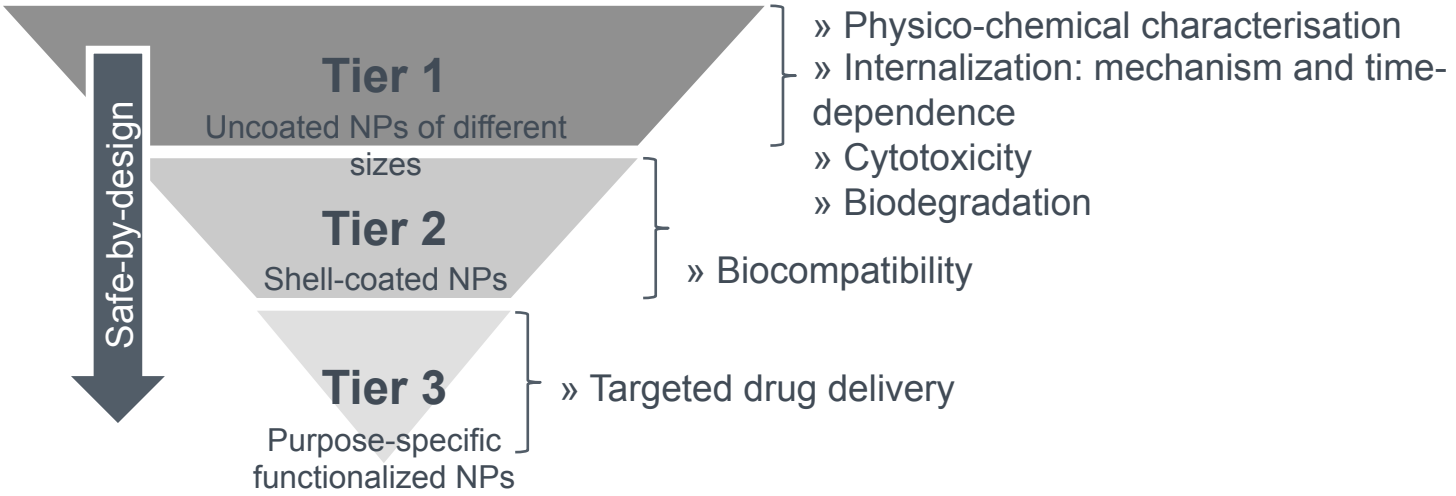
Adapted from Movia D. *et al.,* Biomaterials, 2014, 35, 9, 2543-2557

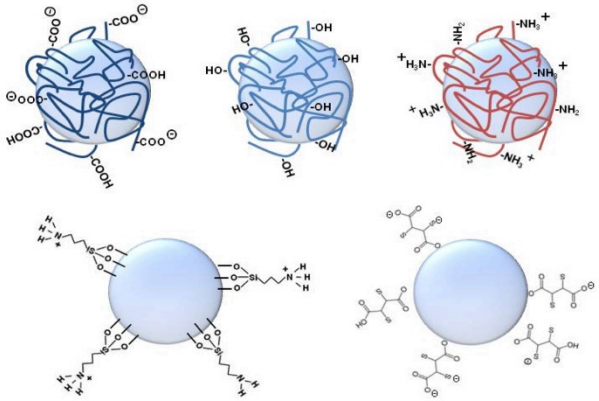
Next NANOTOOL: MULTIFUN





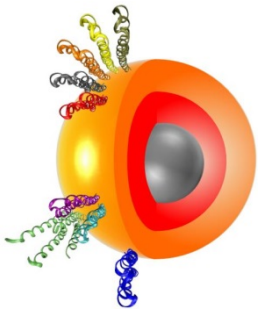
Theranostic tool cancer treatment





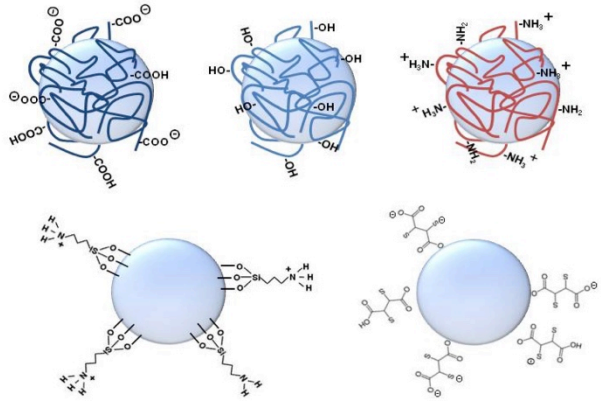
MF66
MF66-N6L
MF66-DOX
MF66-N6L-DOX
MF66-POS

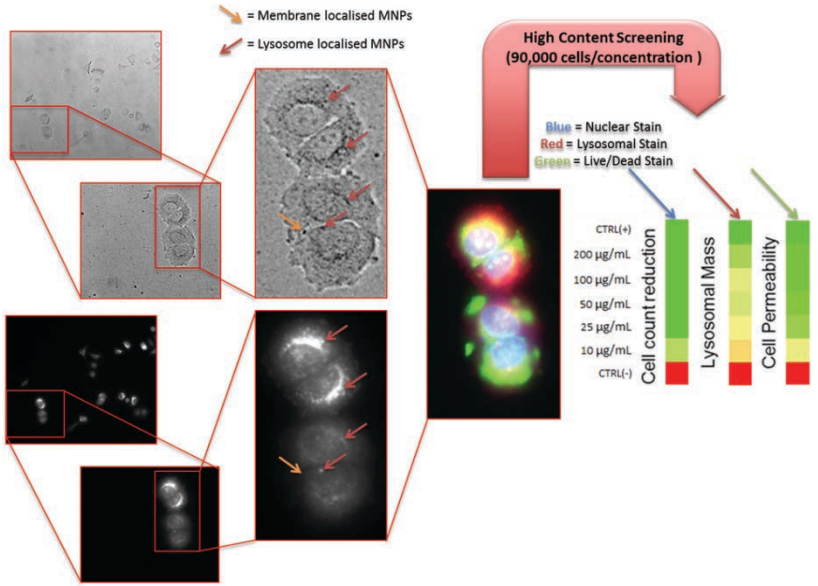
What is the best Functional SPION for Theranostic application?

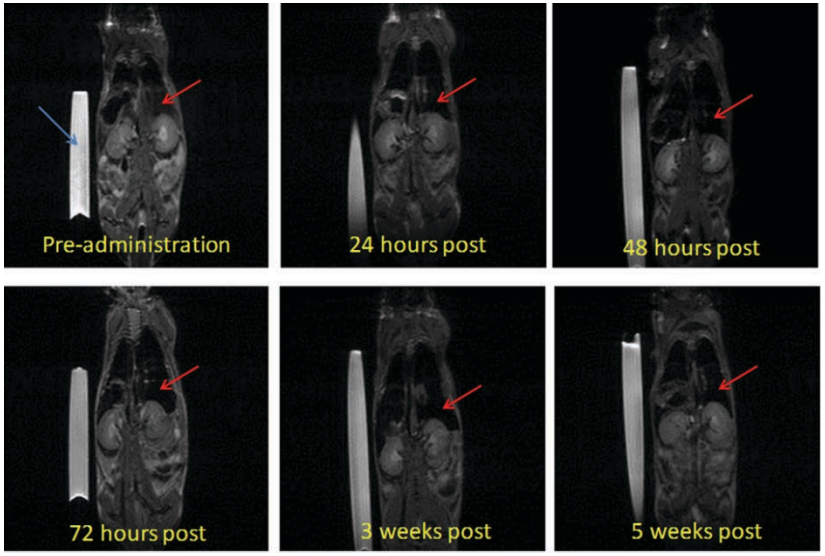


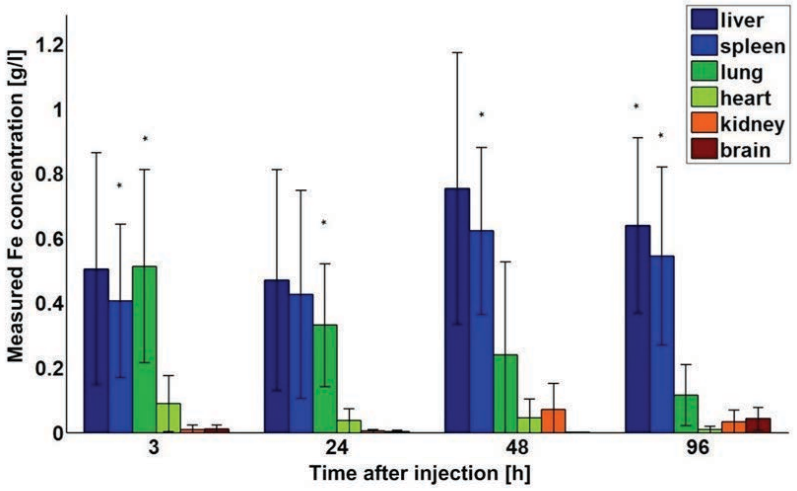
Source: Kossatz et al., 2015, Breast Cancer Research

SPION applied to cancer treatment



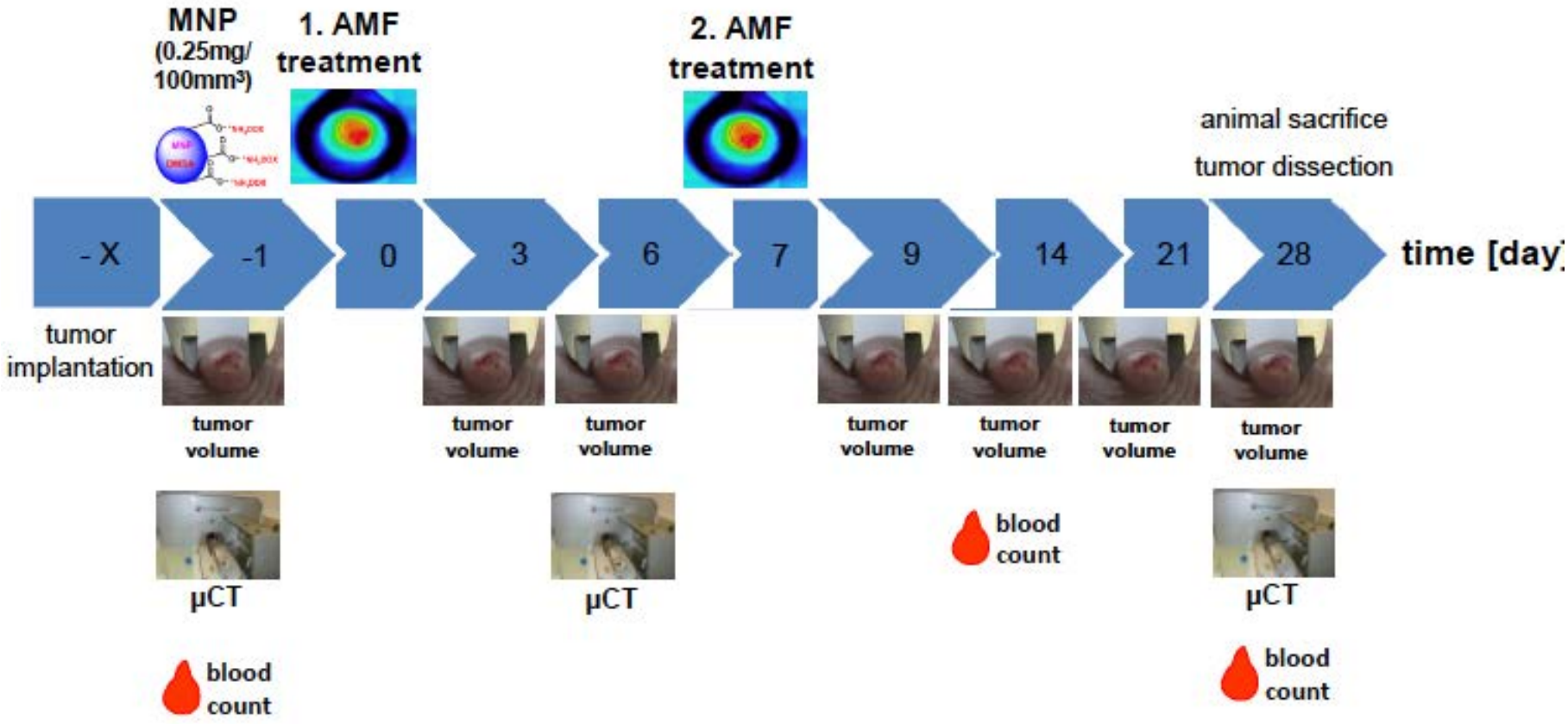






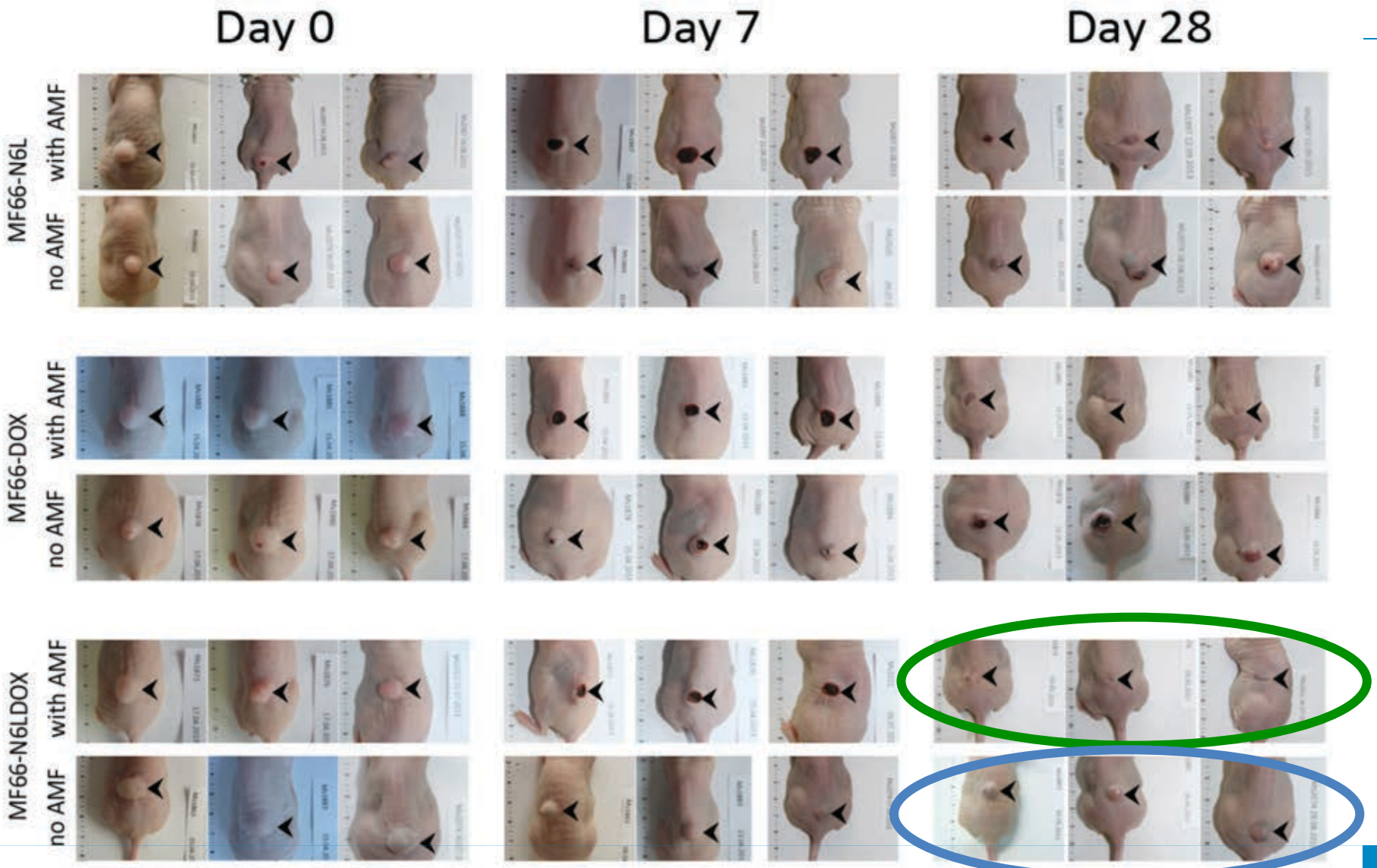
Gobbo et al., Theranostics, 2015 and Nanomedicine 2015; Crosbie-Staunton K. et al, submitted 2015; PhD to be submitted Nov 2015

SPION applied to cancer treatment



Source: Kossatz et al., 2015, Breast Cancer Research

Theranostic tools for cancer treatment



Kossatz et al., 2015, Breast Cancer Research

NANOMEDICINE AT TCD
Scientific Outputs

Nanomedicine: Nanotechnology, Biology, and Medicine
xx (2015) xxx–xxx

nanomedjournal.com

Nanomedicine applied to translational oncology: A future perspective on cancer treatment

Lisa Bregoli, PhD[a], Dania Movia, PhD[b], James D. Gavigan-Imedio, MSc[c], Joanne Lysaght, PhD[d], John Reynolds, MD PhD[d], Adriele Prina-Mello, MSc PhD[e,b,*]

Theranostics 2015, Vol. 5, Issue 11 1249

IVYSPRING INTERNATIONAL PUBLISHER

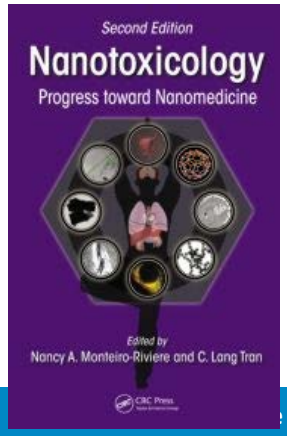
Theranostics

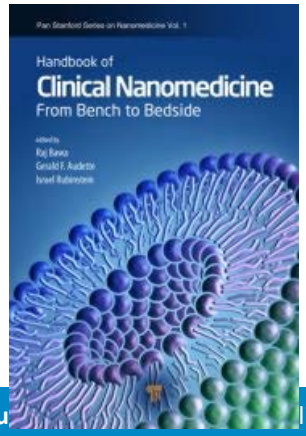
2015; 5(11): 1249-1263. doi: 10.7150/thno.11544

Review

Magnetic Nanoparticles in Cancer Theranostics

Oliviero L. Gobbo[1,2], Kristine Sjaastad[3], Marek W. Radomski[1,4,5], Yuri Volkov[3,6] and Adriele Prina-Mello[3,6]





Nano Today (2015) 10, 274–277

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nanotoday

NEWS AND OPINIONS

The role of biological monitoring in nano-safety

Enrico Bergamaschi[a,*], Craig Poland[b,1], Irina Guseva Canu[c,2], Adriele Prina-Mello[d,3]

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Leading opinion

A safe-by-design approach to the development of gold nanoboxes as carriers for internalization into cancer cells

Dania Movia[a], Valerie Gerard[a,c], Ciaran Manus Maguire[b], Namrata Jain[b], Alan P. Bell[d], Valeria Nicolosi[a,c,e], Tiina O'Neill[f], Dimitri Scholz[f], Yurii Gun'ko[a,c], Yuri Volkov[a,b], Adriele Prina-Mello[a,b,*]

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Nanotechnologies for the study of the central nervous system

A. Ajetunmobi[a,b], A. Prina-Mello[a,b,1,*], Y. Volkov[a,b], A. Corvin[c], D. Tropea[c,1,**]

BASIC SCIENCE

Nanomedicine: Nanotechnology, Biology, and Medicine
11 (2015) 815–824

Original Article

nanomedjournal.com

Cellular uptake and biocompatibility of bismuth ferrite harmonic advanced nanoparticles

Davide Staedler[a,1], Solène Passemard, MSc, PhD[a,1], Thibaud Magouroux, MSc, PhD[b], Andrii Rogov, MSc[b], Ciaran Manus Maguire, MSc[c], Bashir M. Mohamed, PhD[c], Sebastian Schwung, MSc[d], Daniel Rytz, MSc, PhD[d], Thomas Jüstel, MS, PhD[e], Stéphanie Hwu, MSc[b], Yannick Mugnier, MSc, PhD[f], Ronan Le Dantec, MSc, PhD[f], Yuri Volkov, MD, PhD[c,g], Sandrine Gerber-Lemaire, MSc, PhD[a], Adriele Prina-Mello, MSc, PhD[c,g], Luigi Bonacina, MSc, PhD[b,*], Jean-Pierre Wolf, MSc, PhD[b]

Solving unmet medical needs: nano-products

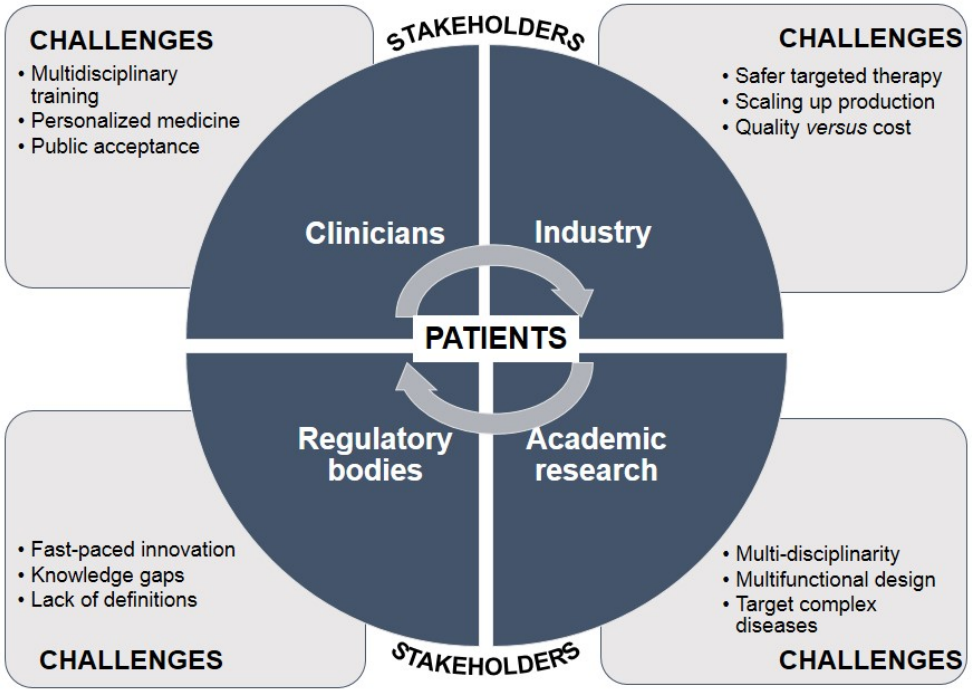
- New Diagnostics
- More Efficient drugs
- New Therapeutics
- New Combination Therapy
- Personalised Therapies

→ Nanomedicine brings breakthrough solutions for the diagnosis and treatment of the most critical diseases

230 nanomedicine products are currently under development, thereof 49 are commercialised (+36% since 2008)

(source Bionest Partners 2013)

Embracing the "NANO" challenges for better treatment to patients

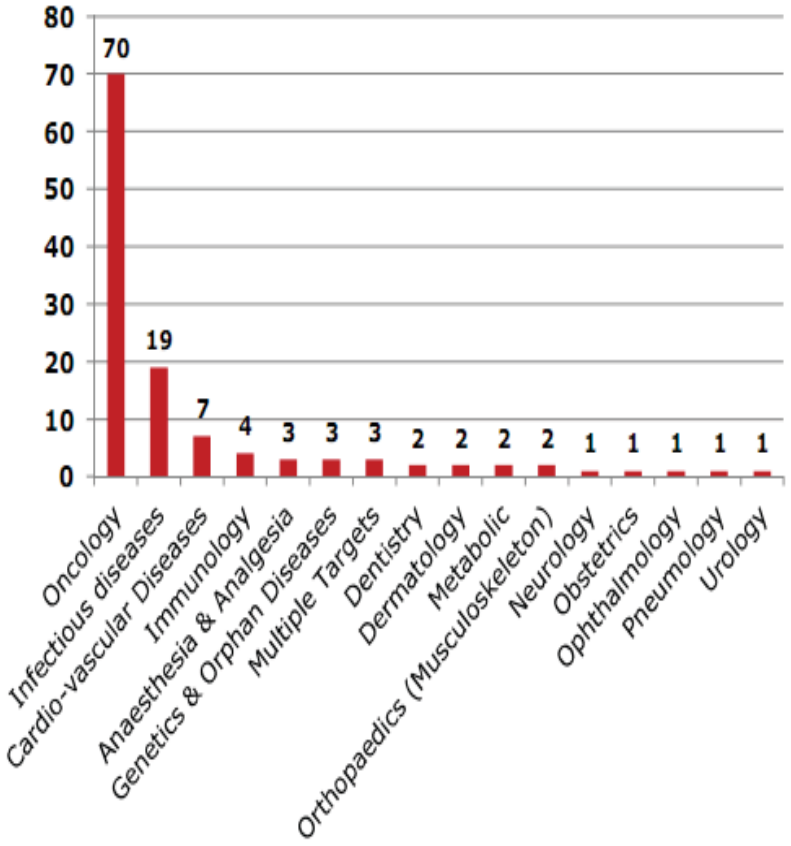


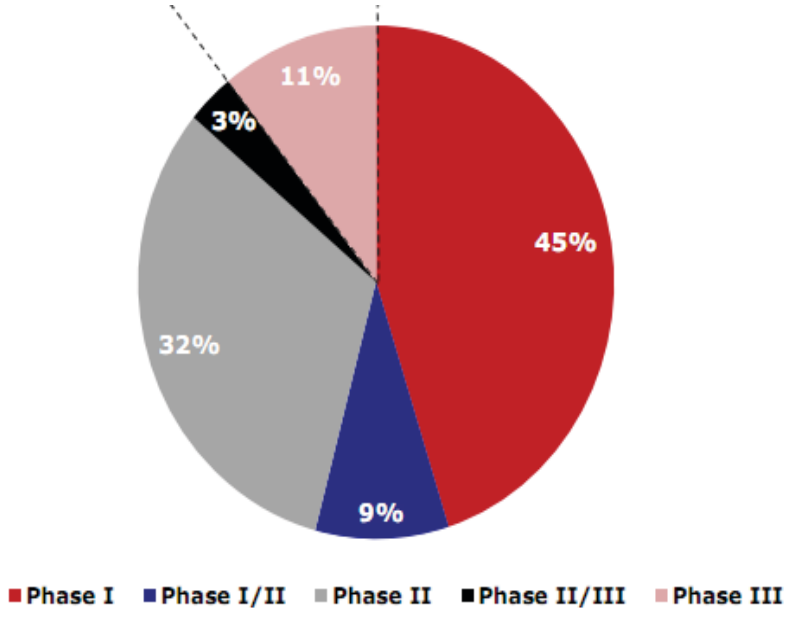
The creation of **a sustainable infrastructure, education and resources** across the nanomedicine value chain is therefore a must do in order to maximise the impact to **Society**

Bregoli et al, 2015, Nanomedicine (Elsevier)

Nanomedicine Pipeline

122 PRODUCTS UNDER CLINICAL DEVELOPMENT





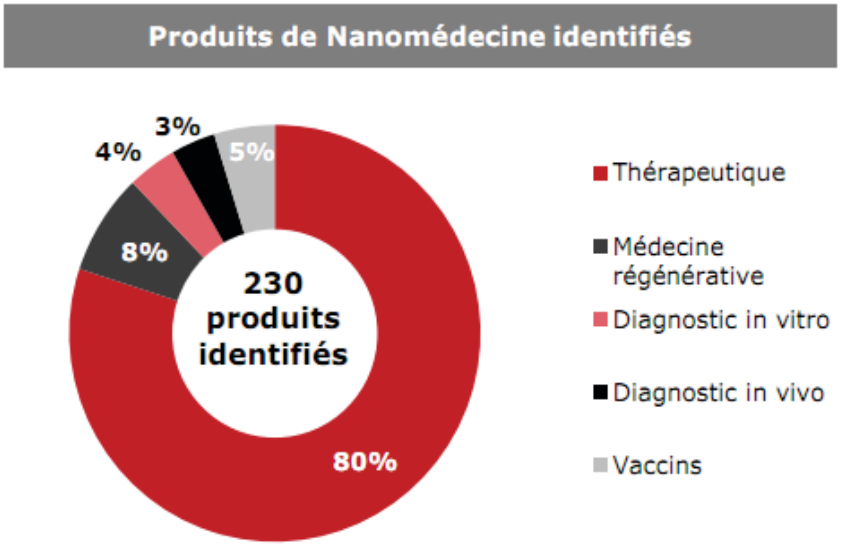
57% effort is in oncology

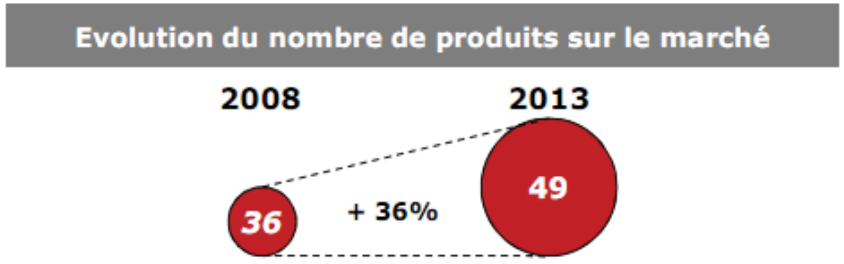
14% in phases II/III et III

Nanomedicine Pipeline

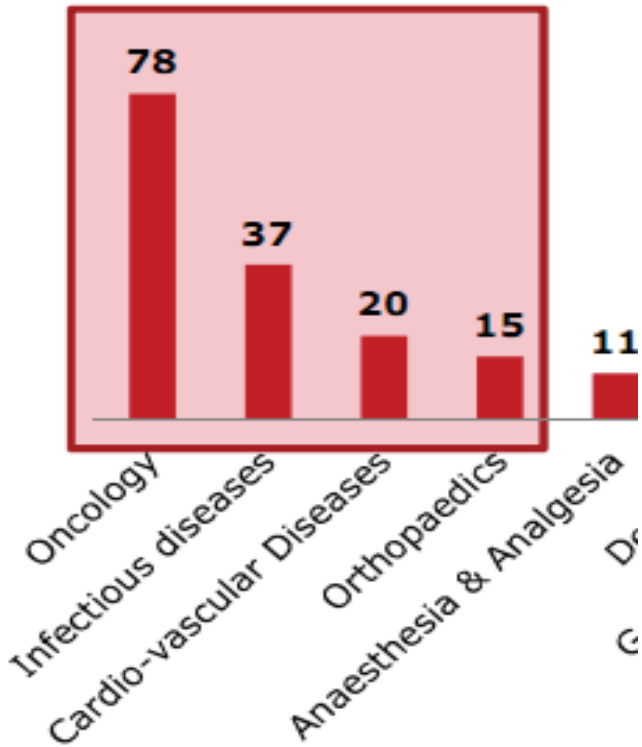
230 NANOPRODUCTS

165 drugs and 65 medical devices

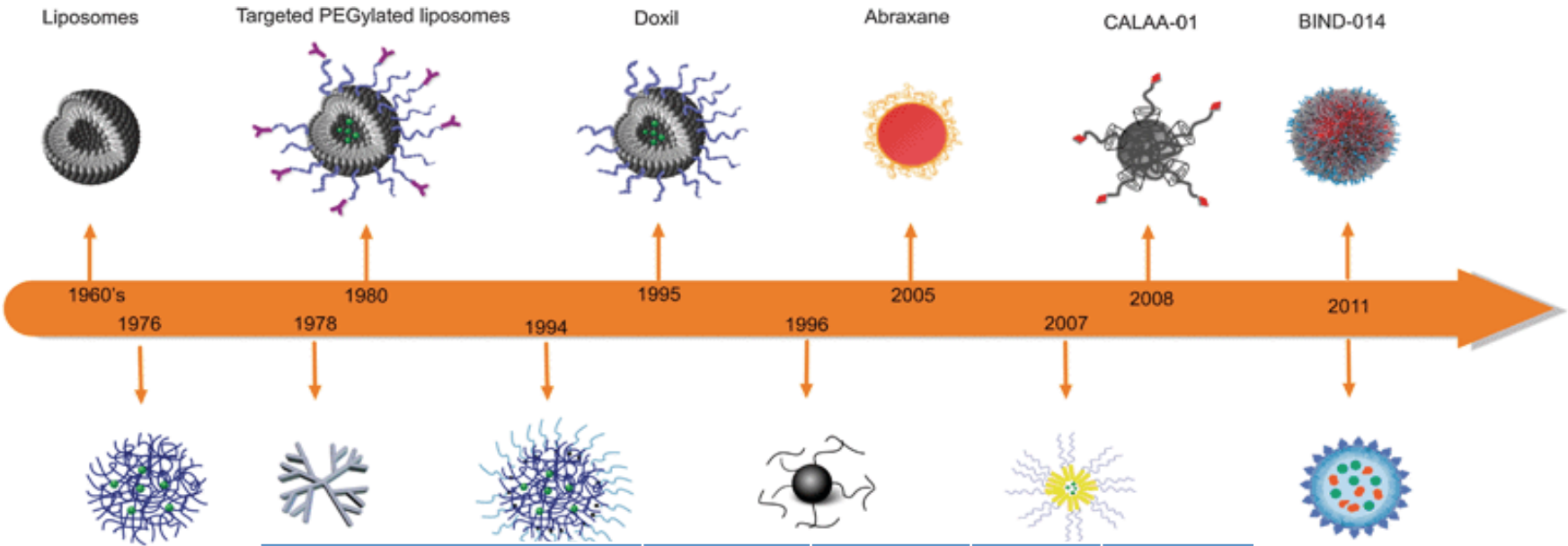




70% of products in the four areas of oncology, infectious diseases, cardiovascular and orthopedics



Global market towards 2020

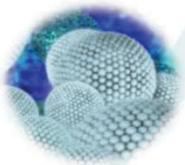


	2010 ($bln)	2011	2020	CAGR (%)
Nanomedicine Global	43.2	50.1	96.9	**14.1**
Cancer Nanomedicine	11.7	14.0	29.5	**16.1**
CNS BBB	0.012	0	0.5	**99.3**

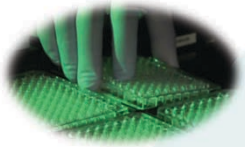
Source: BBC Research

THE NANOMEDICINE INFRASTRUCTURE: ENABLING INNOVATION AND CONFIDENCE

EUNCL
Nanomedicine Characterisation Laboratory

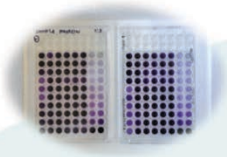


Candidate nanomedicine



Prescreen
-Zeta potential,
-Size distribution
-Endotoxin
-Stability

PCC
- Size
- Surface potential
- Purity
- Surface morphology
- Composition
....



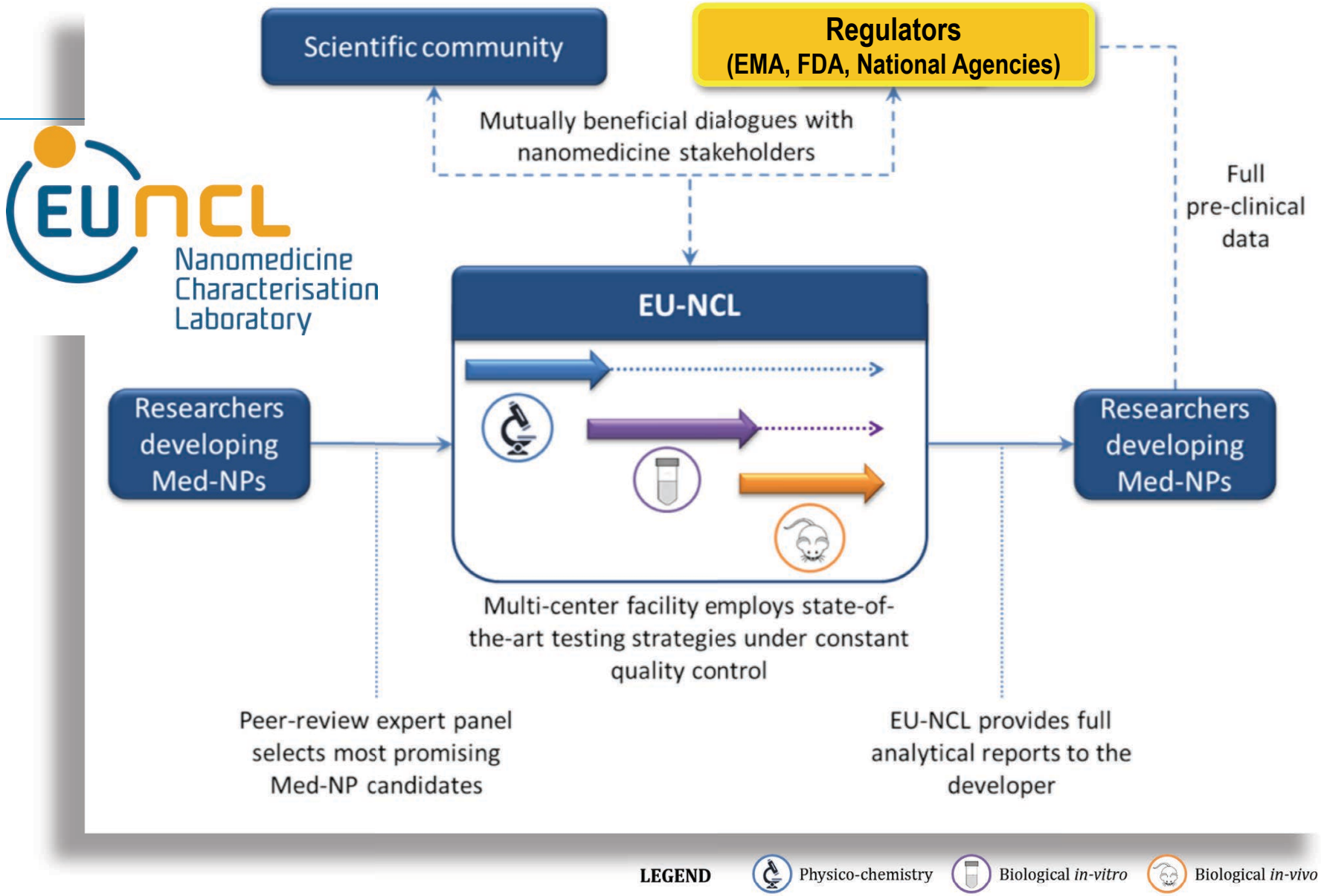
In vitro
Haematology/ Immunology/ Cytotoxicity
- Oxidative stress,
- Membrane permeability
- Mitochondrial dysfunction
- Complement Activation
- Coagulation properties
- Hemolytic properties
-…

In vivo
-PK Biodistribution
-Immunogenicity Toxicity
-Pharmakokinetic
…

Final report

Source: WWW.EUNCL.EU

EUNCL TRANSLATIONAL APPROACH



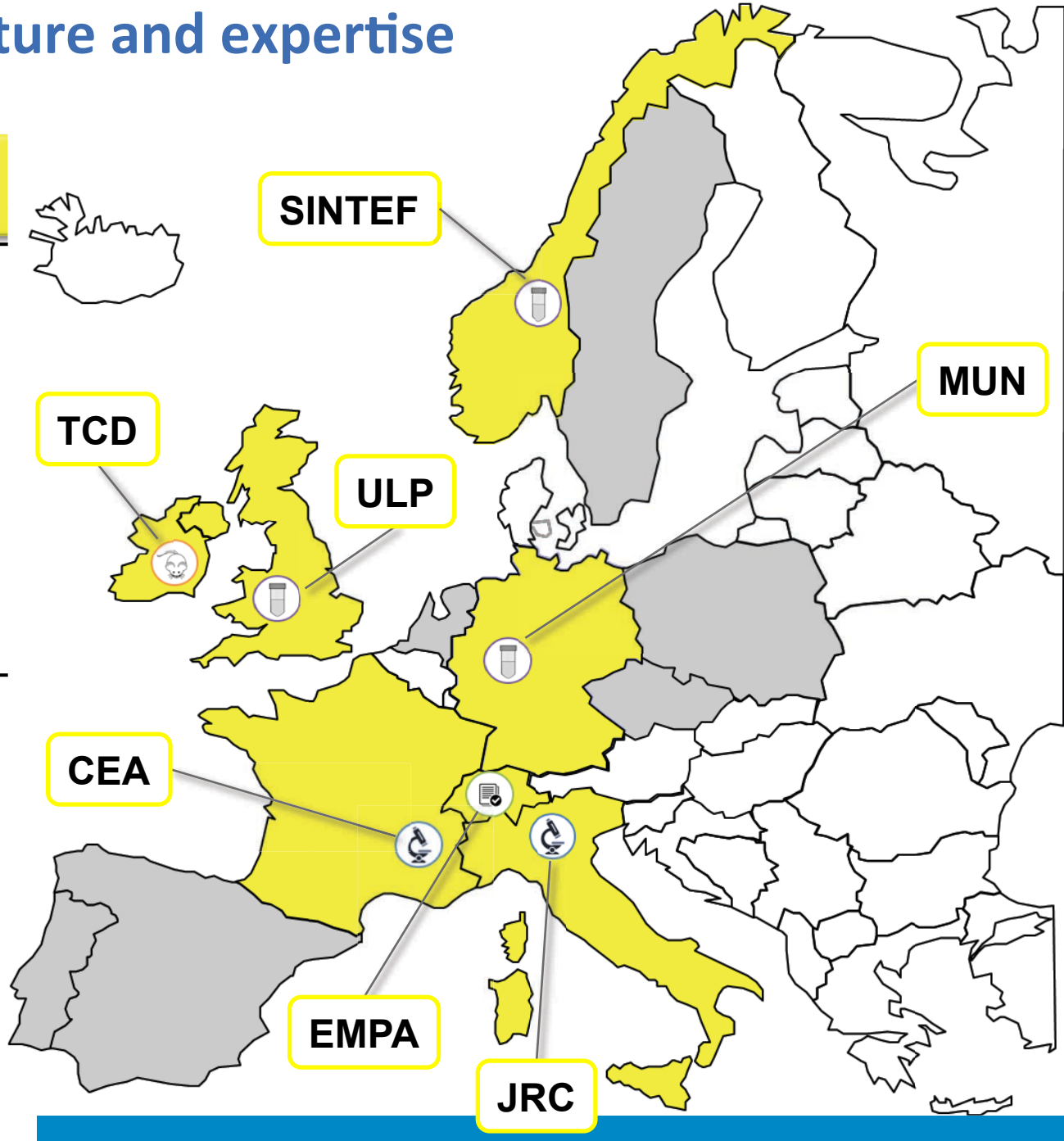
Source: WWW.EUNCL.EU

EU-NCL: infrastructure and expertise

Expertise of the consortium partners

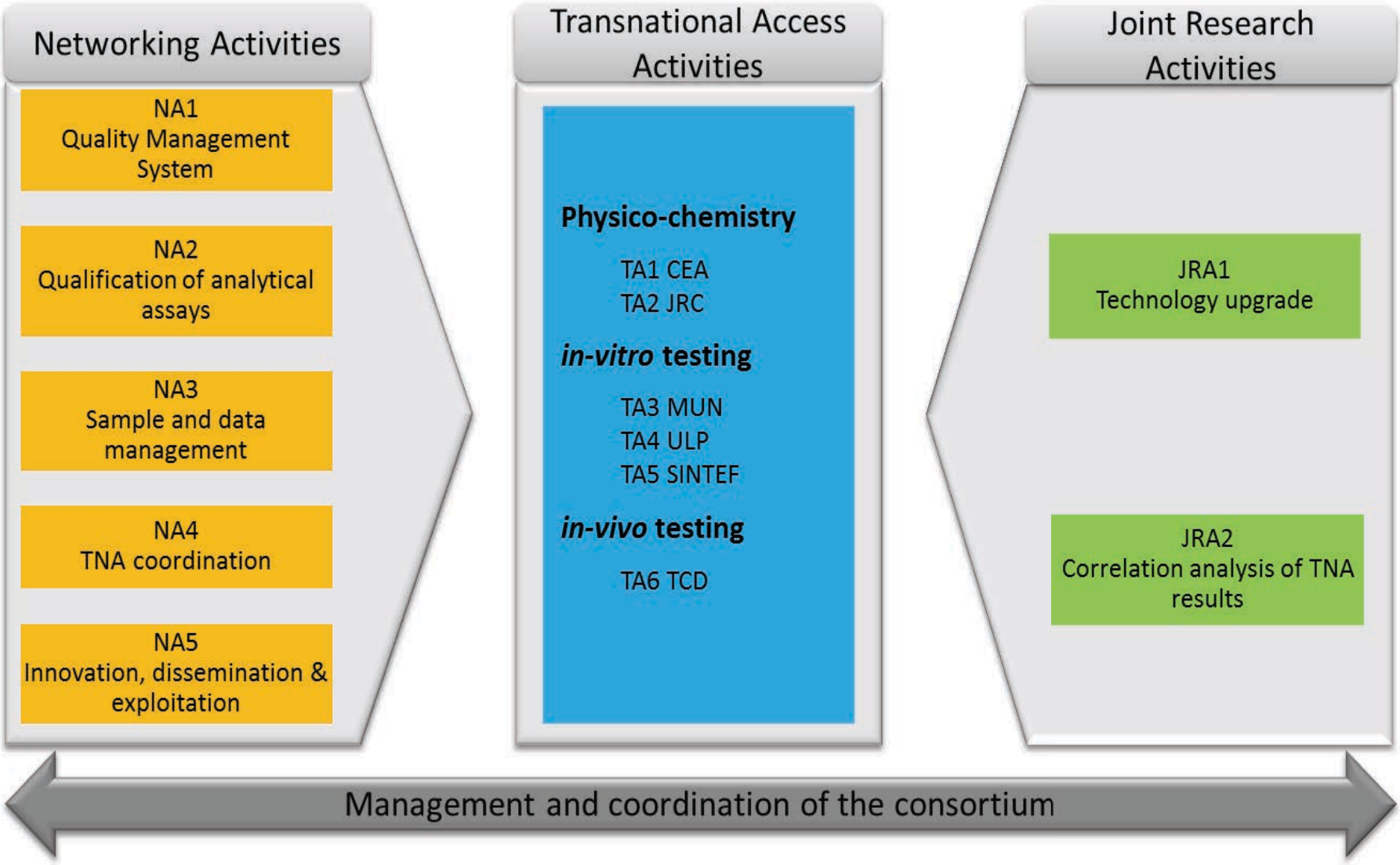
- Physico-chemistry
- Biological *in-vitro*
- Biological *in-vivo*
- Quality

EUNCL Nanomedicine Characterisation Laboratory

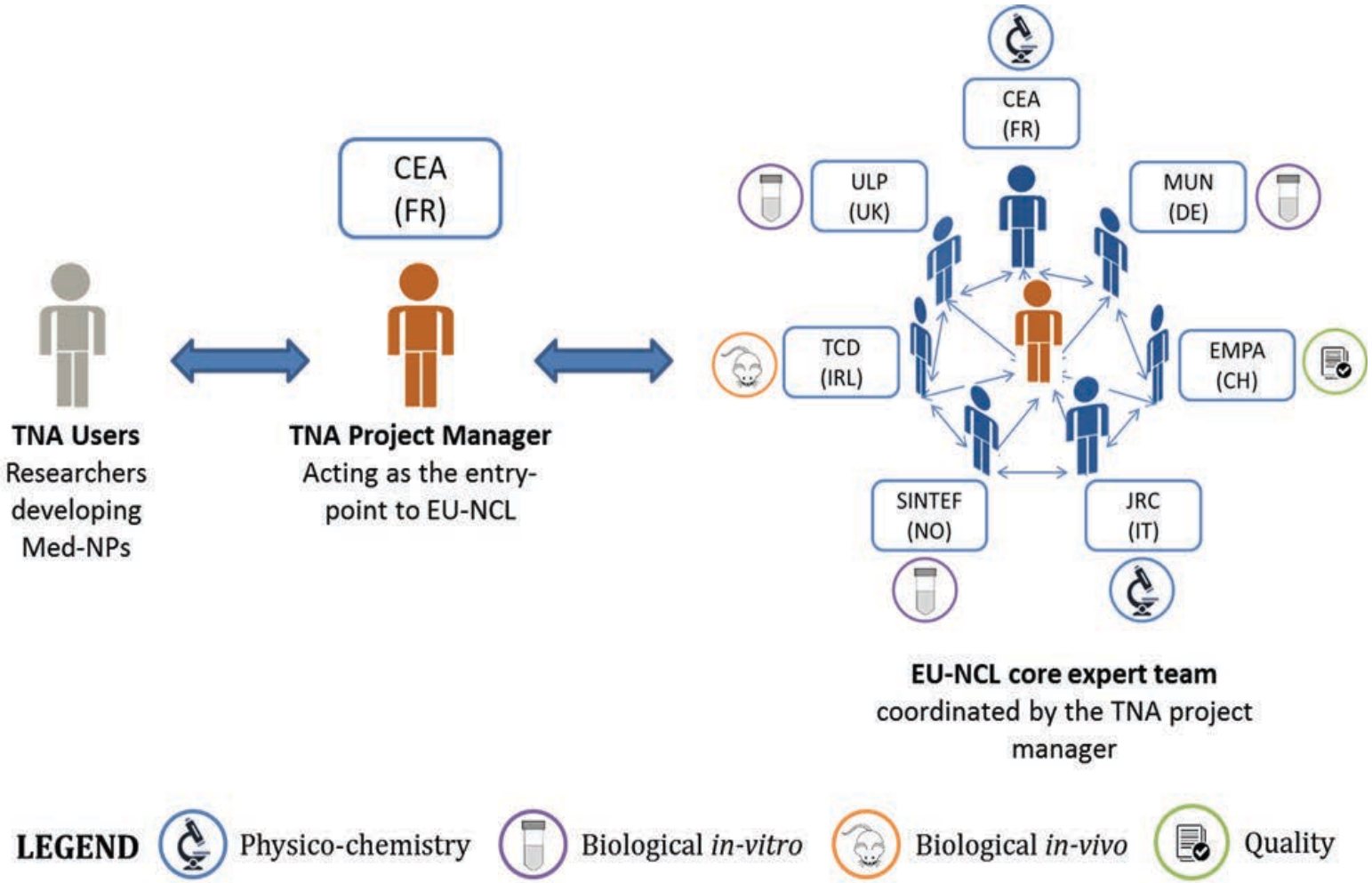


Source: WWW.EUNCL.EU

The 3 main groups of activities of EU-NCL

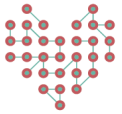


OPENING THE TRANSNATIONAL ACCESS SOON: WATCH THE SPACE IN 2016



Source: WWW.EUNCL.EU

Acknowledgements



- **Nanomedicine Group at Trinity College Dublin**
- **All Collaborators**
- **Funding agencies**

This work has been partially funded under the EU FP7 programme under the NAMDIATREAM, MULTIFUN, NANoREG, AMCARE, QNANO projects and H2020 EU-NCL.

This work is partially funded under the Amber centre and CRANN institute by Science Foundation Ireland.

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Thank You for your attention

Questions?

For more information:
E: ***prinamea@tcd.ie; prinamea@gmail.com***
P. +353 1 896 3259
Linkedin: adriele-prina-mello/1/393/b13
Google scholars: Adriele Prina-Mello
Research Gate profile: Adriele_Prina-Mello