Master 2 Pharmacotechnie et Biopharmacie

Communication Scientifique

Simona Mura | September 11, 2024 |

Outline

Organization of research

Building a bibliography

Communicating scientific results

Ethical principles

Organization of research

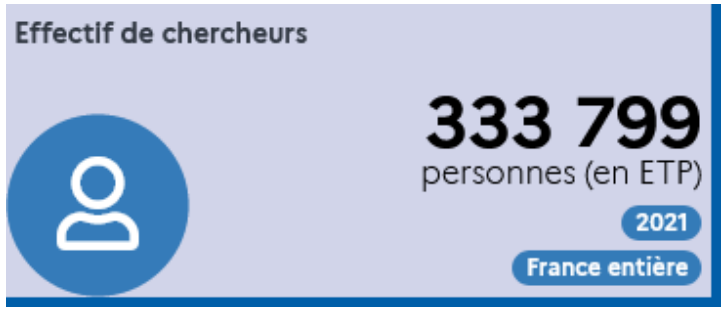
industry and public institutions

Public research

- Administrations
- Organized and financed by the French government and local authorities

Private research

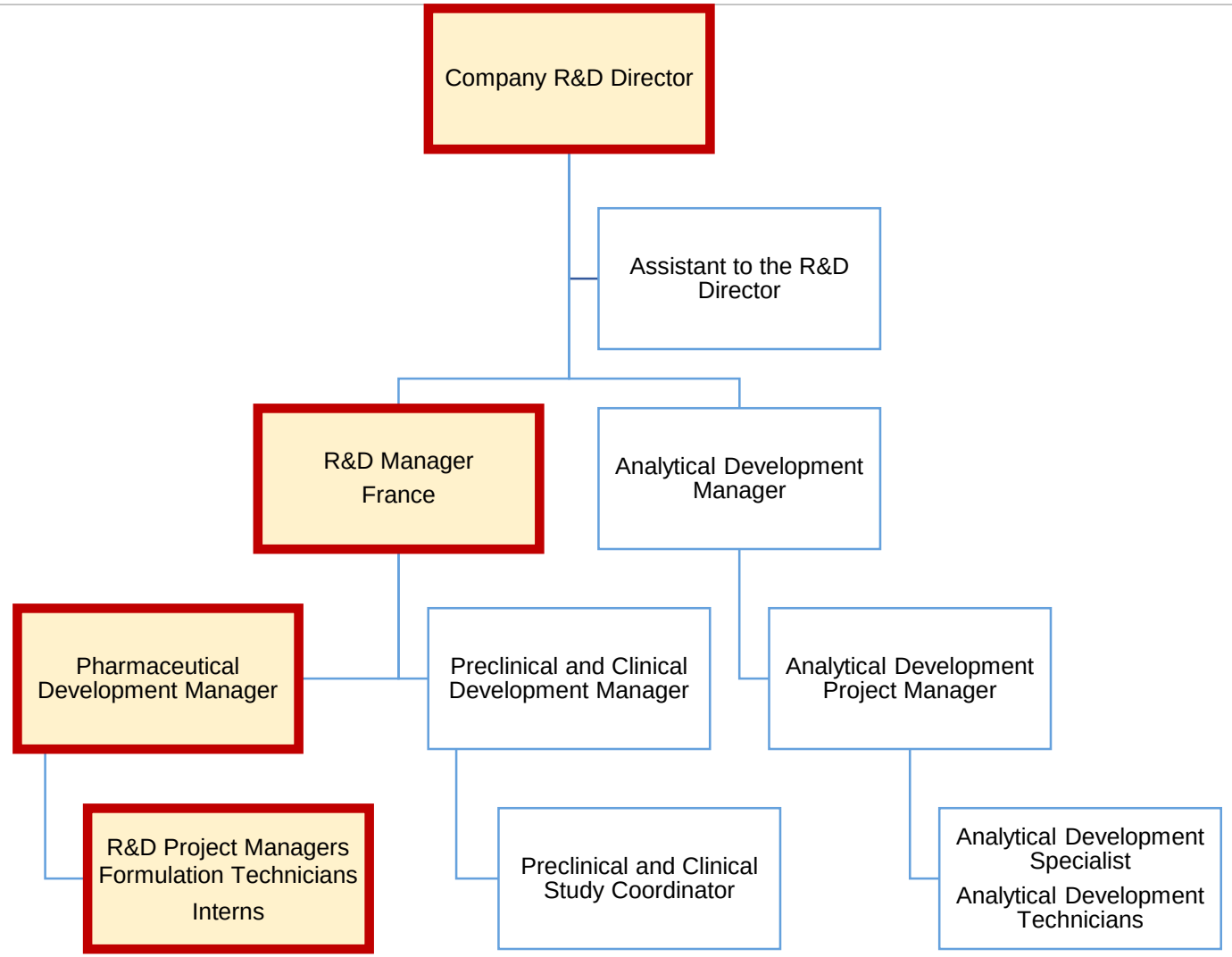
- Enterprises
- Financed by private companies



https://publication.enseignementsup-recherche.gouv.fr/eesr/FR/T497/les_moyens_humains_de_la_recherche_et_developpement/#ILL_EESR16_R_35_01

Organization of research

R&D industrial unit



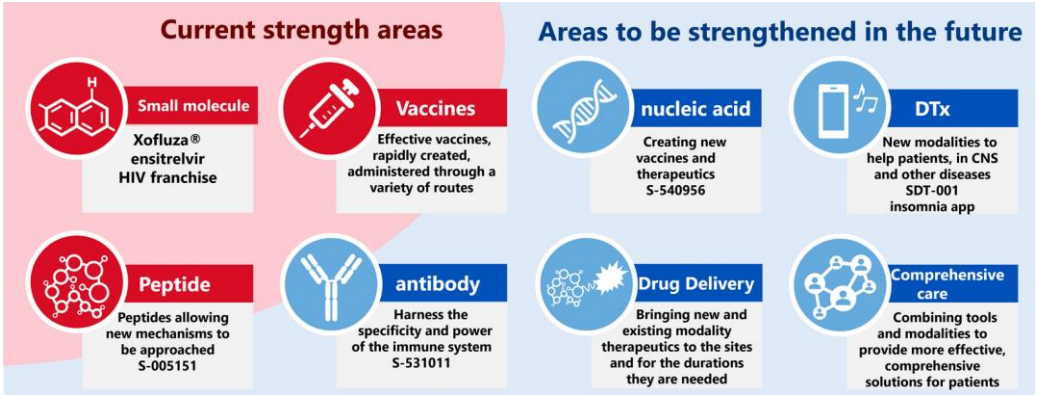
Responsable Développement pharmaceutique

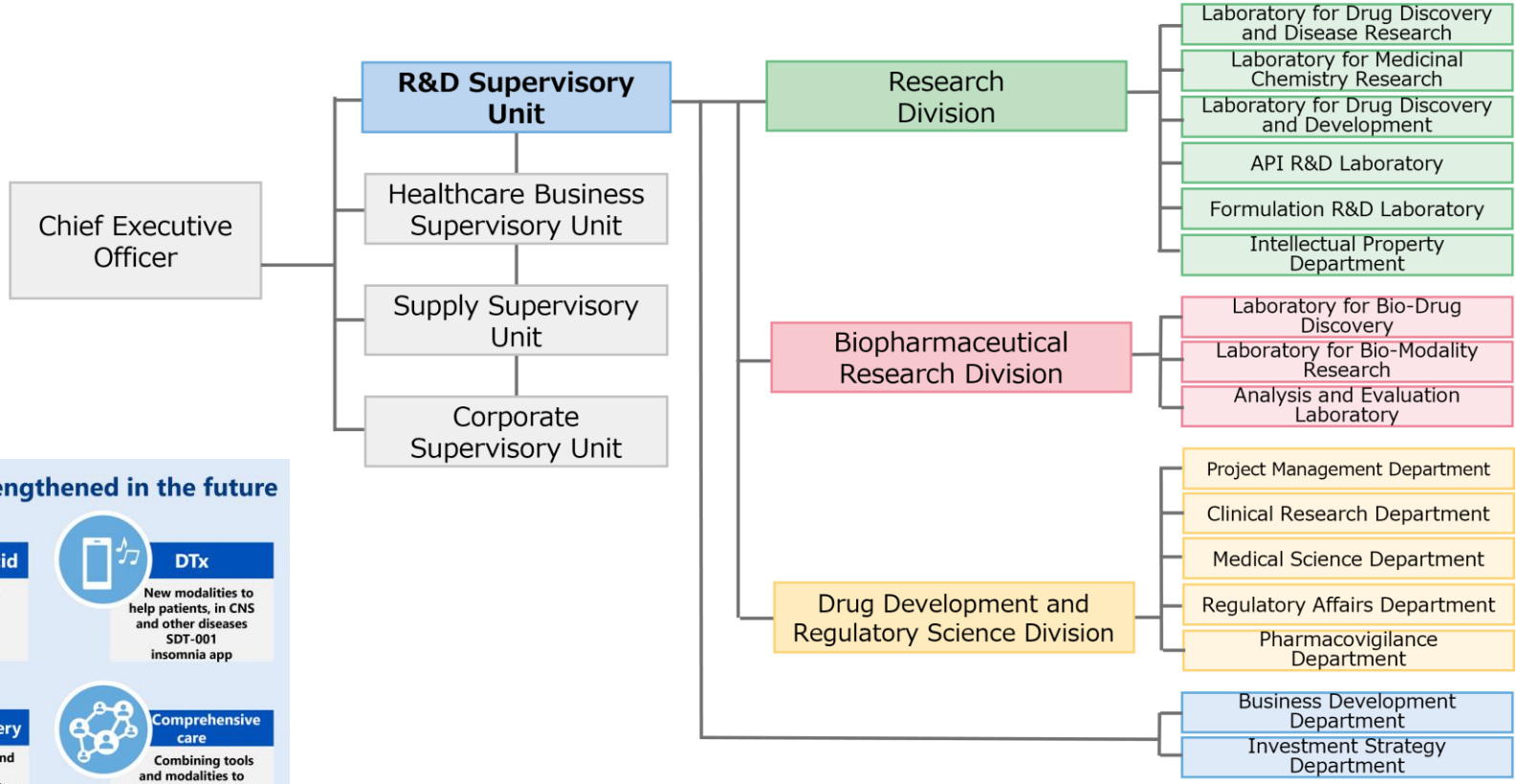
Chargés de projets R&D

Organization of research

R&D industrial unit

"Creating the future of healthcare with new platforms"





https://www.shionogi.com/global/en/innovation/randd/overview-of-randd/randd-vision-and-strategy.html

Organization of research

Public research in France

Centre National de la Recherche Scientifique

Institut national de la santé et de la recherche médicale

Institut national de recherche pour l'agriculture, l'alimentation et l'environnement

Commissariat à l'Énergie Atomique et aux Énergies Alternatives

Centre national d'études spatiales

Major research organizations

- Multidisciplinary (CNRS)
- Targeted (INSERM, INRAE, INRIA, CEA, CNES)
- Foundations (Institut Pasteur and Institut Curie)

EPST

- Public scientific and technological establishments
- Staff are civil servant

EPIC

- Public industrial and commercial establishments
- Staff are private-sector employees

Organization of research

Public research in France

Organization of research

Public research in France

université PARIS-SACLAY

Organization of research

Public research in France

cnrs
Inserm
INRAE
Inria
INSTITUT PASTEUR
institut Curie
cea
cnes

université PARIS-SACLAY

BioCIS
ICSN
icp
ICMMO
ISMO
Institut Galien PARIS-SACLAY
NeuroPSI
scanR

Organization of research

Research units

Affiliated with a higher education institution or one or more research organizations

Created by decision of French Ministry of Higher Education and Research (MESR) for 5 years

Unité propre de recherche

- Managed directly by a unique research organization

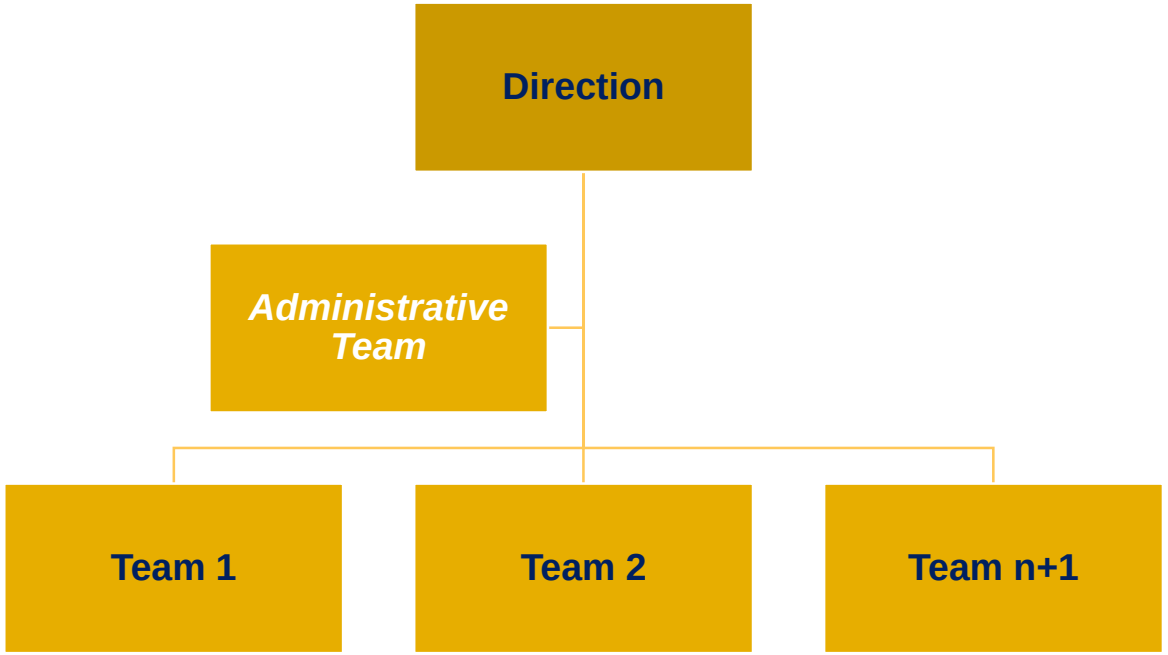
Unité mixte de recherché (UMR)

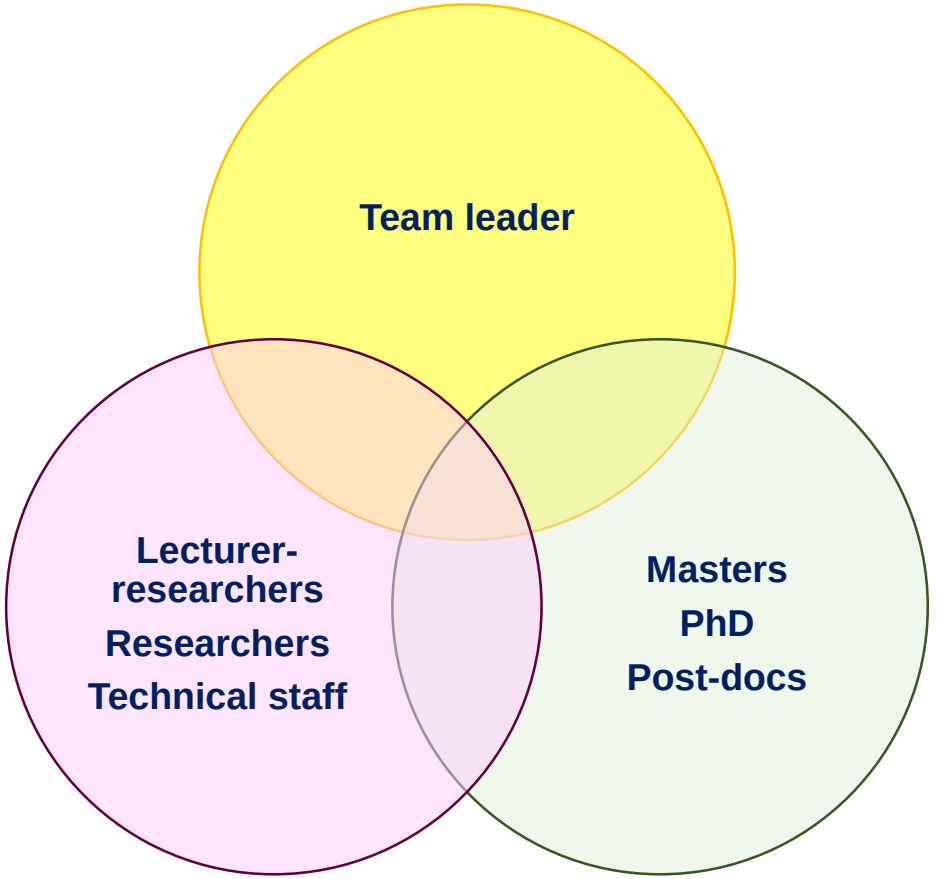
- Created through collaboration agreement
- Involves higher education and scientific/technological establishments
- Based on approved research project
- Co-managed by governing authorities (e.g., CNRS, INSERM)
- Authorities provide resources (human, material, financial)

https://publication.enseignementsup-recherche.gouv.fr/eesr/FR/T497/les_moyens_humains_de_la_recherche_et_developpement/#ILL_EESR16_R_35_01

Organization of research

Research units





Organization of research

Research units

Camille Galap
President
Université Paris-Saclay

Jacques Maddaluno
Director
Institut de chimie

INSTITUT GALIEN PARIS-SACLAY
UMR 8612

Directrice : Myriam TAVERNA
Directeur adjoint : Nicolas TSAPIS

Conseil de laboratoire
Conseil des chefs d'équipe

Chargé·e·s de missions
Assistante Prévention : Laurence MOINE
Communication : Anaïs PITTO-BARRY
Correspondante formation : Catherine CAILLEAU
Relations Internationales : Jean-Philippe MICHEL
Relations Entr. & Valorisation : Elias FATTAL
Développement Soutenable : Hervé HILLAIREAU
Qualité de Vie au Travail : Anaïs PITTO-BARRY

Administratrice	Gestion - Administration	Secrétaire de Direction	Administrateur SI
Gwénaëlle LO BUE (AI) BAP J	Patricia LIVET (T) 90% BAP J Maria DA SILVA (T) 50% BAP J *Julie EGUIENTA (T) 50% BAP J*	Carole CHOQUET (T) 80% BAP J	Léon BOUILLET (IE) 50%* BAP E

Plateformes scientifiques

Caractérisation de nano-objets	Biologie	Analytique	Biophysique et instrumentation
Julie MOUGIN (IE) – 25% N… (AI)	Catherine CAILLEAU (IE) – 90% *Mélanie HERY (AI) – 40%**	Lynda BENRABAH (AI) – 90% N… (AI)	David CHAPRON (IE) – 50% *Safa MOHAMED ISMAIL (AI) – 40%* N… (AI) – 50%

Organigramme
CNRS
Université Paris-Saclay
CDD

50%* : avec UMR 8076 Biomolécules : Conception, Isolement, Synthèse

1-2 MULTIPHASE
Vincent FAIVRE (PR)
Angelina ANGELOVA (DR)
David CHAPRON (IE) – 50%
François-Xavier LEGRAND (MC)
Ali MAKKY (MC)
Jean-Philippe MICHEL (MC)
N… AI – 50%

3 Physique Pharmaceutique
Florence AGNELY (PR)
Bertrand FOURNIER (MC)
Sandrine GEIGER (MC)
Tristan GIRAUD (MC)
Nicolas HUANG (PR)
Ghozlène MEKHLOUFI (MC)
Safa MOHAMED ISMAIL (AI) – 10%

4 PNAS
Myriam TAVERNA (PR)
Lynda BENRABAH (AI) – 10%
Abdul ISMAIL (CPJ)
Thanh-Duc MAI (MC)
Sameh OBEID (MC)
Claire SMADJA (PR)
Thuy TRAN-MAIGNAN (MC)
N… (AI) – 10%

5 INPACT
Elias FATTAL (PR)
Nicolas TSAPIS (DR)
Amélie BOCHOT (PR)
Catherine CAILLEAU (IE) – 10%
François FAY (MC)
*Mélanie HERY (AI) – 10%**
Hervé HILLAIREAU (PR)
Laurence MOINE (DR)
Juliette VERGNAUD (MC)

6 Equipe 6
Gilles PONCHEL (PR)
Eloísa BERBEL-MANAIA (MC)

7 NANOMED
Julien NICOLAS (DR)
Nathalie JARROUX (PR)
Sinda LEPETRE (MC)
Julie MOUGIN (IE) – 75%
Simona MURA (PR)
Anaïs PITTO-BARRY (CR)
Mariana VARNA (MC)

ORGANIGRAMME – JUILLET 2024

Organization of research

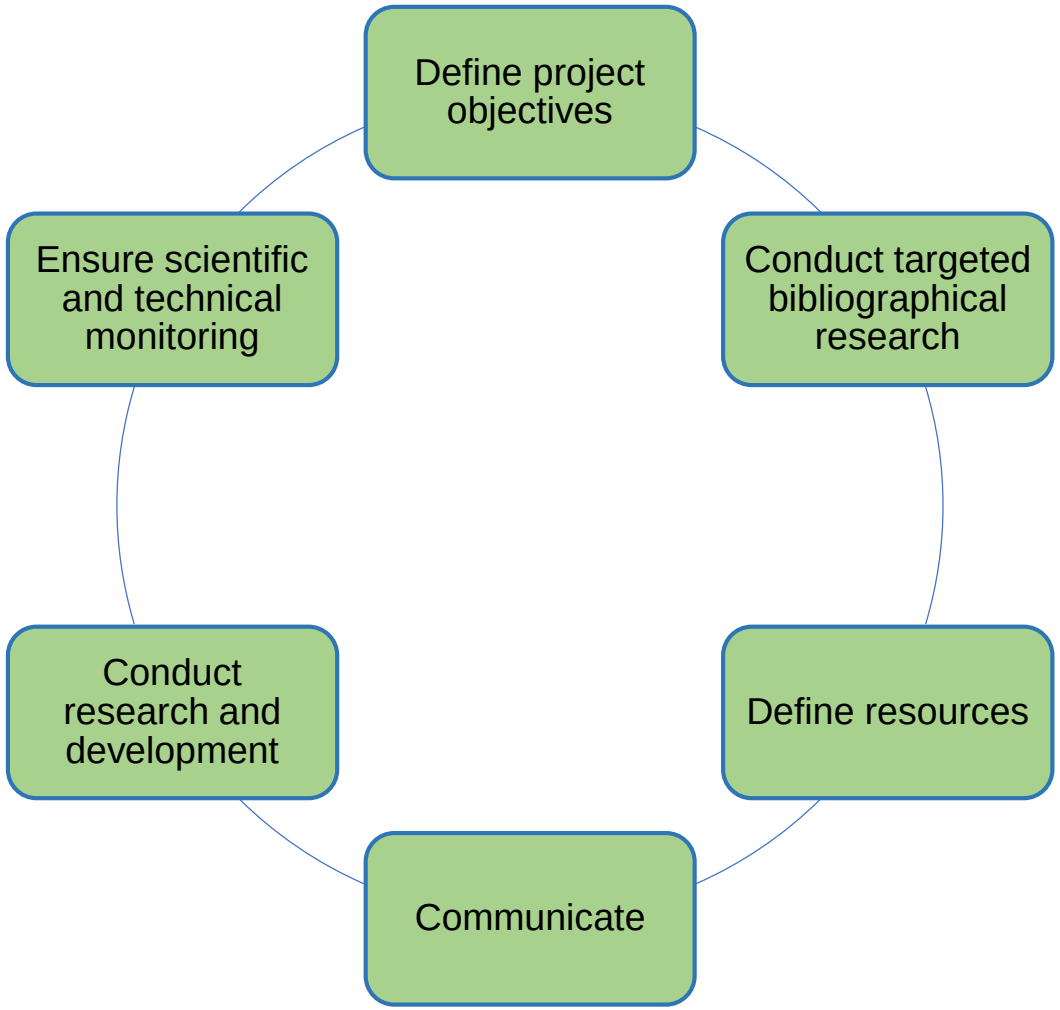
Research units

The laboratory council

- Advisory body
- Composed of and chaired by the unit Director
- Administrative manager
- Elected representatives from each major category
- At least one representative from each research team
- Consulted on all measures relating to the organization and running of the UMR
  - changes to the structure or organization
  - the allocation of budgetary resources
  - human resources policy
  - issues relating to safety and working conditions

Building a bibliography

Essential activities for successful R&D projects



Building a bibliography

Keep up to date with science and technology

Tip #1 Read books and specialized journals

Tip #2 Attend scientific conferences, symposiums, and seminars

Tip #3 Interact with suppliers: request documentation, whitepapers, or technical reports

Tip #4 Participate in online forums, or social media groups dedicated to specific scientific topics

Building a bibliography

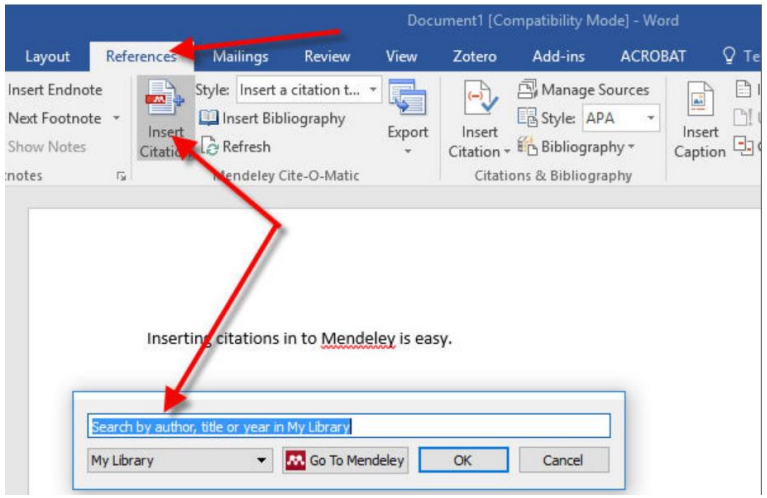
Create your bibliography

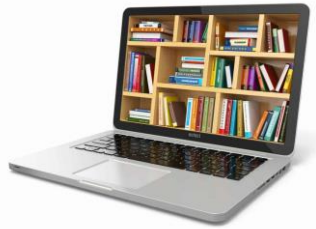
Consult databases

Use tools for managing citations

Build your personal bibliography

Cite while you write





Communicating scientific results

Communication: WHY

Showcasing Progress

- Inform about the progress of research and development projects
- Communicate breakthroughs and significant scientific discoveries

Recognition and interaction

- Gain recognition from peers and broader audience
- Engage with the scientific community

Patent Tracking

- Ensure protection for valuable intellectual property

Align with the main purpose of scientific research

Contribute to human understanding and progress

Communicating scientific results

Communication: Internal

Oral

- Team meetings, discussions, and presentations within the organization
- Facilitates immediate feedback and clarifications
- Audience
  - Colleagues
  - Superiors
  - Subordinates

Written Documents

- Mails, reports, memos, and documentation
- Ensures information is documented for future reference
- Audience
  - Team members
  - Managers
  - Stakeholders

Communicating scientific results

Communication: external

Participation in conferences

Oral presentations or posters

- Shares knowledge
- Disseminates information
- Builds professional connections
- Audience
  - peers
  - experts
  - professionals
  - potential collaborators

Publications

Articles in peer reviewed journals, patents

- Contributes to the knowledge in the field
- Protect unique inventions and innovations
- Audience
  - researchers
  - academics
  - professionals
  - patent offices
  - potential investors & collaborators

Communicating scientific results

Communication: Oral

CRS 2023 #CRS2023
ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 Paris Hotel » Las Vegas, NV, USA
THE FUTURE OF DELIVERY SCIENCE

8:30 AM – 4:00 PM US PST CRS/IPEC Biologics Summit

Moderator: Ron Smith, PhD – Pharmawyze, LLC

Speaker: Simon Matoori, PhD – Université de Montréal
Montreal, Canada

Speaker: Nigel Langley

Speaker: Beate Bittner, PhD – F. Hoffmann - La Roche

Speaker: Marie Printz (she/her/hers) – Halozyme, Inc.

Speaker: Deborah Bitterfield, PhD (she/her/hers) – Lindy Biosciences

Speaker: Patrick Doyle, PhD (he/him/his) – MIT

Speaker: Rick Fitch, PhD (he/him/his) – Xeris Pharmaceuticals, Inc.

Speaker: Ryan Nolan, PhD – Halozyme Therapeutics

Speaker: Manuel Sanchez-Felix, PhD – Novartis Institutes for BioMedical Research

Speaker: Hao Lou, PhD (he/him/his) – UNIVERSITY OF KANSAS

Communicating scientific results

Communication: Oral

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Speaker: Manuel Sanchez-Felix, PhD – Novartis Institutes for BioMedical Research

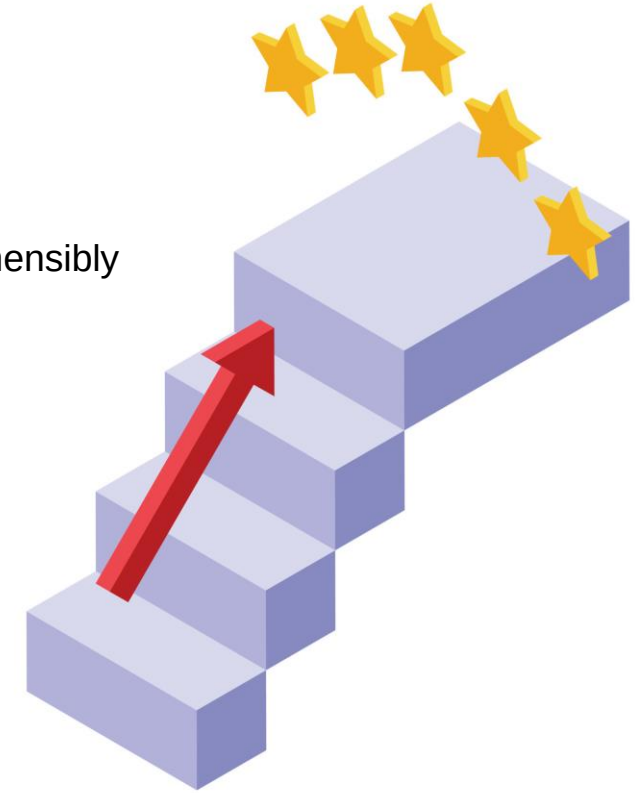
Speaker: Hao Lou, PhD (he/him/his) – UNIVERSITY OF KANSAS

10 – 15 minutes

Communicating scientific results

Communication: Oral

Conclusions
- State what has been demonstrated
- Summarize the key takeaways



Results
- Present compelling results
- Convey the main points concisely
- Be sure data and findings are presented comprehensibly

Aim of the Work
- Emphasize why your work matters
- Convince the audience of the significance of the research
- Keep it concise (1 minute) and clear

Introduction
- Set the context of the work, especially for non-specialists.
- Capture the audience attention
- Keep it simple

Communicating scientific results

Communication: poster

2014 conference of the American Geophysical Union (AGU)

Communicating scientific results

Communication: poster

Succinctly summarize research findings

Visual elements enhance understanding Attract attention

Interactive Engagement

Benefits

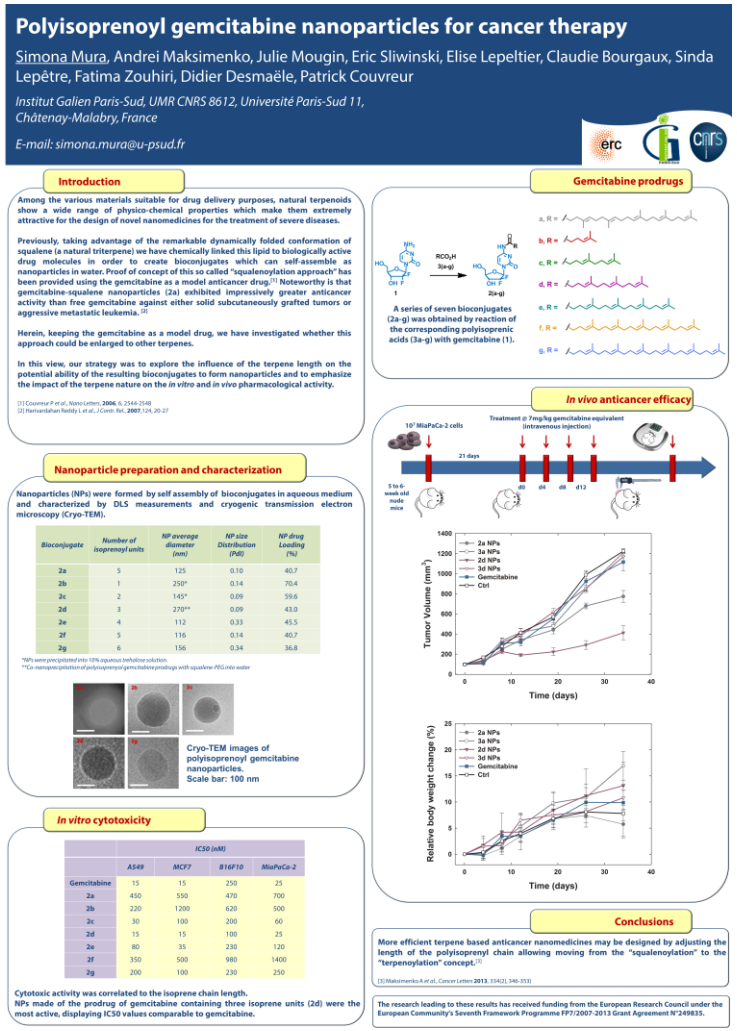
- Communicates complex ideas effectively
- Encourages collaboration and networking
- Enables immediate feedback and peer review
- Offers researchers the opportunity to present their work

Impact

- Enhances the visibility of research
- Facilitates knowledge exchange
- Promotes interdisciplinary learning
- Enhances the for participant conference experience

Communicating scientific results

Communication: poster



Polyisoprenoyl gemcitabine nanoparticles for cancer therapy

Simona Mura, Andrei Maksimenko, Julie Mougin, Eric Sliwinski, Elise Lepeltier, Claudie Bourgaux, Sinda Lepêtre, Fatima Zouhiri, Didier Desmaële, Patrick Couvreur

Institut Galien Paris-Sud, UMR CNRS 8612, Université Paris-Sud 11, Châtenay-Malabry, France

E-mail: simona.mura@u-psud.fr

Introduction

Among the various materials suitable for drug delivery purposes, natural terpenoids show a wide range of physico-chemical properties which make them extremely attractive for the design of novel nanomedicines for the treatment of severe diseases.

Previously, taking advantage of the remarkable dynamically folded conformation of squalene (a natural triterpene) we have chemically linked this lipid to biologically active drug molecules in order to create bioconjugates which can self-assemble as nanoparticles in water. Proof of concept of this so called "squalenoylation approach" has been provided using the gemcitabine as a model anticancer drug.[1] Noteworthy is that gemcitabine-squalene nanoparticles (2a) exhibited impressively greater anticancer activity than free gemcitabine against either solid subcutaneously grafted tumors or aggressive metastatic leukemia. [2]

Herein, keeping the gemcitabine as a model drug, we have investigated whether this approach could be enlarged to other terpenes.

In this view, our strategy was to explore the influence of the terpene length on the potential ability of the resulting bioconjugates to form nanoparticles and to emphasize the impact of the terpene nature on the *in vitro* and *in vivo* pharmacological activity.

[1] Couvreur P et al., *Nano Letters*, **2006**, 6, 2544-2548
[2] Harivardhan Reddy L et al., *J Contr Rel.*, **2007**, 124, 20-27

Gemcitabine prodrugs

A series of seven bioconjugates (2a-g) was obtained by reaction of the corresponding polyisoprenic acids (3a-g) with gemcitabine (1).

Nanoparticle preparation and characterization

Nanoparticles (NPs) were formed by self assembly of bioconjugates in aqueous medium and characterized by DLS measurements and cryogenic transmission electron microscopy (Cryo-TEM).

Bioconjugate	Number of isoprenoyl units	NP average diameter (nm)	NP size Distribution (PdI)	NP drug Loading (%)
2a	5	125	0.10	40.7
2b	1	250*	0.14	70.4
2c	2	145*	0.09	59.6
2d	3	270**	0.09	43.0
2e	4	112	0.33	45.5
2f	5	116	0.14	40.7
2g	6	156	0.34	36.8

*NPs were precipitated into 10% aqueous trehalose solution.
**Co-nanoprecipitation of polyisoprenoyl gemcitabine prodrugs with squalene-PEG into water

Cryo-TEM images of polyisoprenoyl gemcitabine nanoparticles. Scale bar: 100 nm

***In vivo* anticancer efficacy**

Treatment @ 7 mg/kg gemcitabine-equivalent (intravenous injection)

Tumor Volume (mm^3) — Time (days)

Relative body weight change (%) — Time (days)

***In vitro* cytotoxicity**

	IC50 (nM)			
	A549	MCF7	B16F10	MiaPaCa-2
Gemcitabine	15	15	250	25
2a	450	550	470	700
2b	220	1200	620	500
2c	30	100	200	60
2d	15	15	100	25
2e	80	35	230	120
2f	350	500	980	1400
2g	200	100	230	250

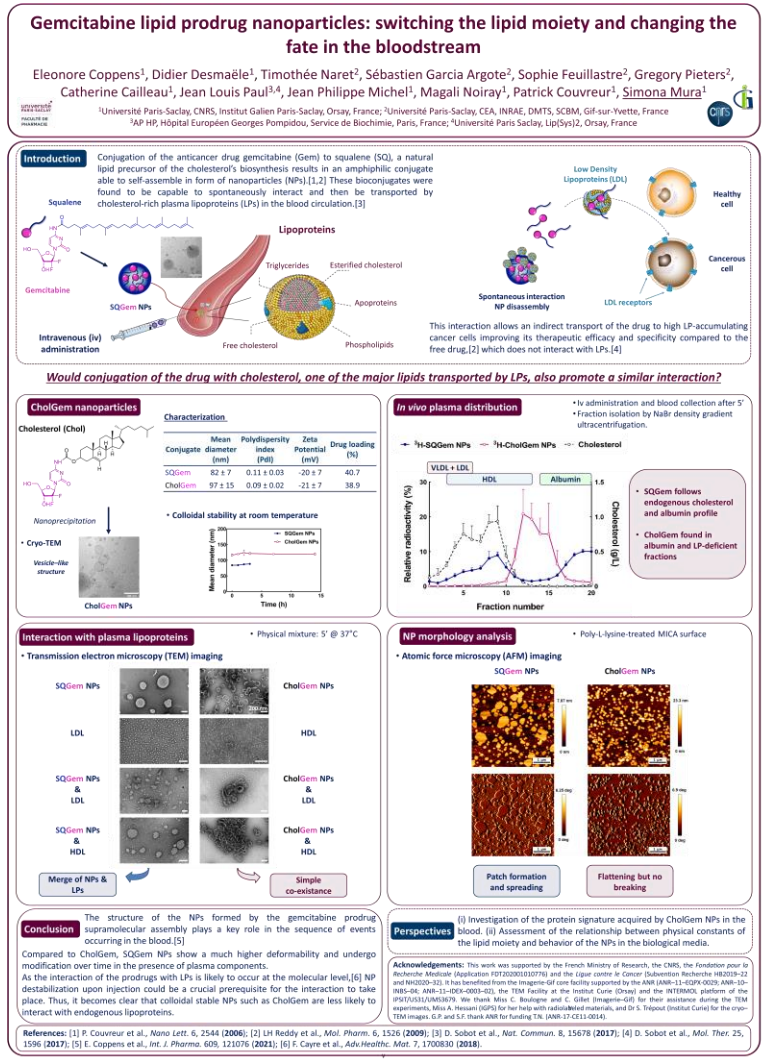
Cytotoxic activity was correlated to the isoprene chain length. NPs made of the prodrug of gemcitabine containing three isoprene units (2d) were the most active, displaying IC50 values comparable to gemcitabine.

Conclusions

More efficient terpene based anticancer nanomedicines may be designed by adjusting the length of the polyisoprenyl chain allowing moving from the "squalenoylation" to the "terpenoylation" concept.[3]

[3] Maksimenko A et al., *Cancer Letters* **2013**, 334(2), 346-353)

The research leading to these results has received funding from the European Research Council under the European Community's Seventh Framework Programme FP7/2007-2013 Grant Agreement N°249835.



Gemcitabine lipid prodrug nanoparticles: switching the lipid moiety and changing the fate in the bloodstream

Eleonore Coppens[1], Didier Desmaële[1], Timothée Naret[2], Sébastien Garcia Argote[2], Sophie Feuillastre[2], Gregory Pieters[2], Catherine Cailleau[1], Jean Louis Paul[3,4], Jean Philippe Michel[1], Magali Noiray[1], Patrick Couvreur[1], Simona Mura[1]

[1]Université Paris-Saclay, CNRS, Institut Galien Paris-Saclay, Orsay, France; [2]Université Paris-Saclay, CEA, INRAE, DMTS, SCBM, Gif-sur-Yvette, France
[3]AP HP, Hôpital Européen Georges Pompidou, Service de Biochimie, Paris, France; [4]Université Paris Saclay, Lip(Sys)2, Orsay, France

Introduction

Conjugation of the anticancer drug gemcitabine (Gem) to squalene (SQ), a natural lipid precursor of the cholesterol's biosynthesis results in an amphiphilic conjugate able to self-assemble in form of nanoparticles (NPs).[1,2] These bioconjugates were found to be capable to spontaneously interact and then be transported by cholesterol-rich plasma lipoproteins (LPs) in the blood circulation.[3]

Squalene — Gemcitabine — SQGem NPs — Intravenous (iv) administration — Lipoproteins — Triglycerides — Esterified cholesterol — Apoproteins — Free cholesterol — Phospholipids

Low Density Lipoproteins (LDL) — Healthy cell — Cancerous cell — LDL receptors — Spontaneous interaction NP disassembly

This interaction allows an indirect transport of the drug to high LP-accumulating cancer cells improving its therapeutic efficacy and specificity compared to the free drug,[2] which does not interact with LPs.[4]

Would conjugation of the drug with cholesterol, one of the major lipids transported by LPs, also promote a similar interaction?

CholGem nanoparticles

Cholesterol (Chol) — Nanoprecipitation — Cryo-TEM — Vesicle-like structure — CholGem NPs

Characterization

Conjugate	Mean diameter (nm)	Polydispersity index (PdI)	Zeta Potential (mV)	Drug loading (%)
SQGem	82 ± 7	0.11 ± 0.03	-20 ± 7	40.7
CholGem	97 ± 15	0.09 ± 0.02	-21 ± 7	38.9

• Colloidal stability at room temperature

Mean diameter (nm) — Time (h) — SQGem NPs — CholGem NPs

***In vivo* plasma distribution**

• Iv administration and blood collection after 5'
• Fraction isolation by NaBr density gradient ultracentrifugation.

^{3}H-SQGem NPs — ^{3}H-CholGem NPs — Cholesterol

VLDL + LDL — HDL — Albumin

Relative radioactivity (%) — Cholesterol (g/L) — Fraction number

• SQGem follows endogenous cholesterol and albumin profile
• CholGem found in albumin and LP-deficient fractions

Interaction with plasma lipoproteins

• Physical mixture: 5' @ 37°C
• Transmission electron microscopy (TEM) imaging

SQGem NPs — CholGem NPs — LDL — HDL — SQGem NPs & LDL — CholGem NPs & LDL — SQGem NPs & HDL — CholGem NPs & HDL

Merge of NPs & LPs — Simple co-existance

NP morphology analysis

• Poly-L-lysine-treated MICA surface
• Atomic force microscopy (AFM) imaging

SQGem NPs — CholGem NPs

Patch formation and spreading — Flattening but no breaking

Conclusion

The structure of the NPs formed by the gemcitabine prodrug supramolecular assembly plays a key role in the sequence of events occurring in the blood.[5]

Compared to CholGem, SQGem NPs show a much higher deformability and undergo modification over time in the presence of plasma components.

As the interaction of the prodrugs with LPs is likely to occur at the molecular level,[6] NP destabilization upon injection could be a crucial prerequisite for the interaction to take place. Thus, it becomes clear that colloidal stable NPs such as CholGem are less likely to interact with endogenous lipoproteins.

Perspectives

(i) Investigation of the protein signature acquired by CholGem NPs in the blood. (ii) Assessment of the relationship between physical constants of the lipid moiety and behavior of the NPs in the biological media.

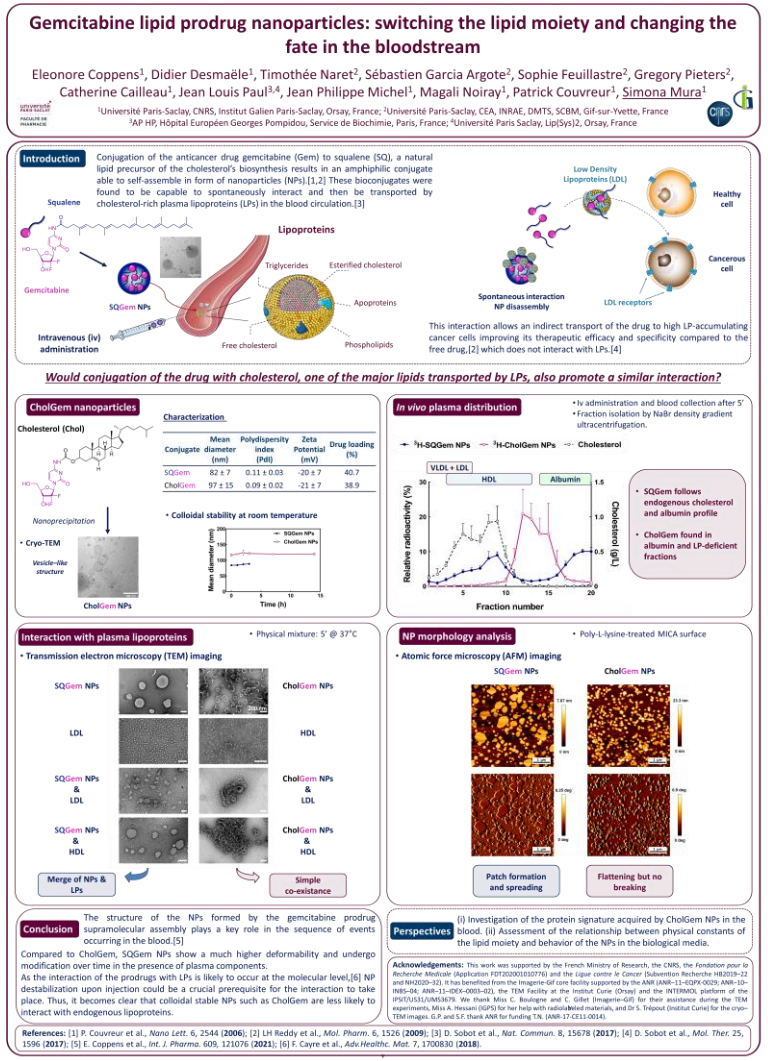
Acknowledgements: This work was supported by the French Ministry of Research, the CNRS, the *Fondation pour la Recherche Medicale* (Application FDT202001010776) and the *Ligue contre le Cancer* (Subvention Recherche HB2019-22 and NH2020-32). It has benefited from the Imagerie-Gif core facility supported by the ANR (ANR–11–EQPX-0029; ANR–10–INBS–04; ANR–11–IDEX–0003–02), the TEM Facility at the Institut Curie (Orsay) and the INTERMOL platform of the IPSIT/I31/UMS3679. We thank Miss C. Boulogne and C. Gillet (Imagerie-Gif) for their assistance during the TEM experiments, Miss A. Hessani (IGPS) for her help with radiolabeled materials, and Dr S. Trépout (Institut Curie) for the cryo-TEM images. G.P. and S.F. thank ANR for funding T.N. (ANR-17-CE11-0014).

References: [1] P. Couvreur et al., *Nano Lett.* 6, 2544 (**2006**); [2] LH Reddy et al., *Mol. Pharm.* 6, 1526 (**2009**); [3] D. Sobot et al., *Nat. Commun.* 8, 15678 (**2017**); [4] D. Sobot et al., *Mol. Ther.* 25, 1596 (**2017**); [5] E. Coppens et al., *Int. J. Pharma.* 609, 121076 (**2021**); [6] F. Cayre et al., *Adv.Healthc. Mat.* 7, 1700830 (**2018**).

Communicating scientific results

Communication: poster

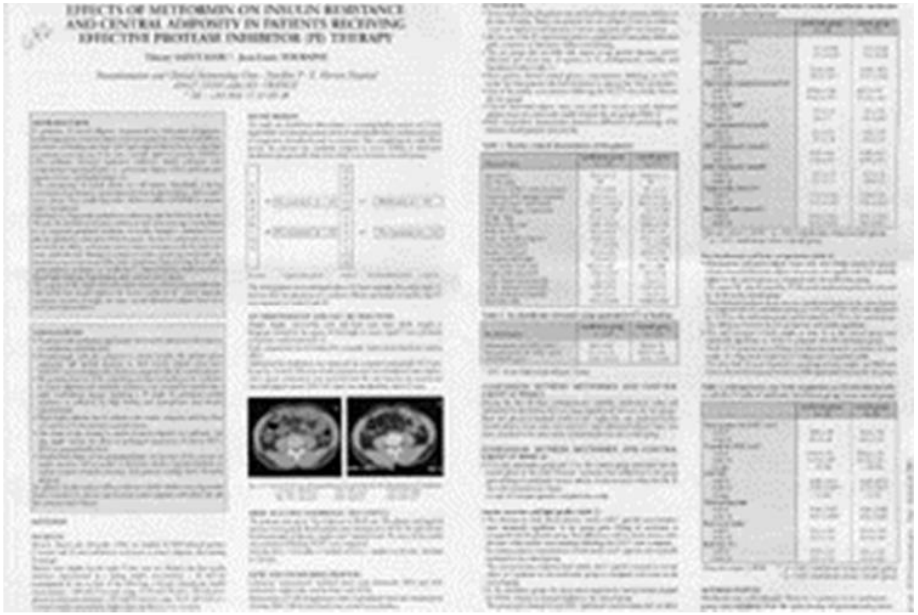
- Visibility and Readability
- Concise and intriguing Title
- Word Count
- Clarity
- Visual Aids
- Layout
- Acknowledgments for funding, collaborators, and institutions



Communicating scientific results

Communication: poster

Don'ts

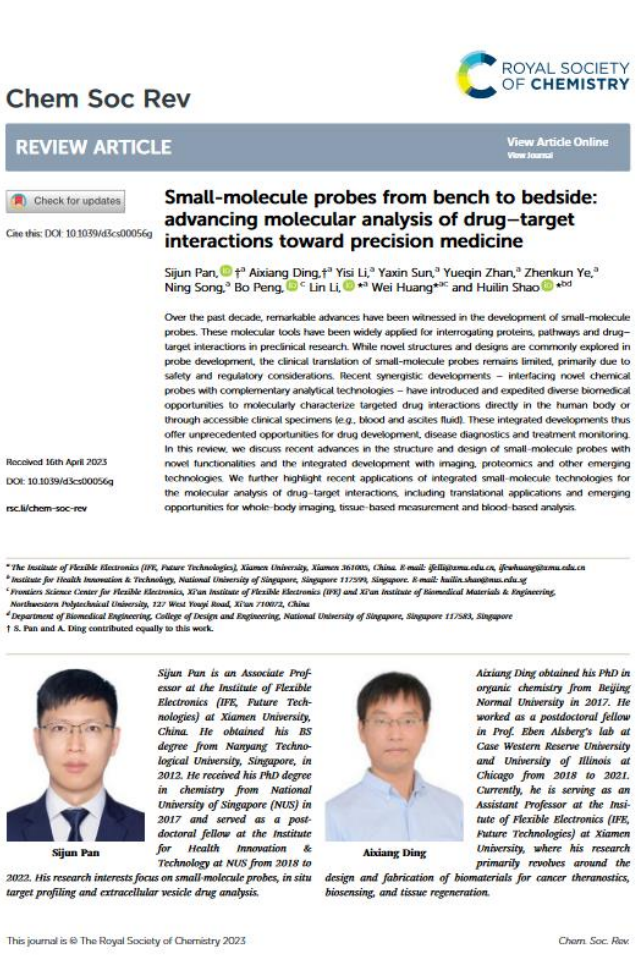


- Overcrowding
- Vague Title
- Lengthy & dense paragraphs
- Chaotic Formatting
- Present only text
- Place information randomly
- Neglect to credit collaborators, funding sources, and your institution

https://www.ncl.ac.uk/academic-skills-kit/assessment/academic-posters/style/

Communicating scientific results

Communication: publications



Chem Soc Rev

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Small-molecule probes from bench to bedside: advancing molecular analysis of drug–target interactions toward precision medicine

Sijun Pan, †[a] Aixiang Ding,†[a] Yisi Li,[a] Yaxin Sun,[a] Yueqin Zhan,[a] Zhenkun Ye,[a] Ning Song,[a] Bo Peng, [c] Lin Li, *[a] Wei Huang*[a,c] and Huilin Shao [a,b,d]

Over the past decade, remarkable advances have been witnessed in the development of small-molecule probes. These molecular tools have been widely applied for interrogating proteins, pathways and drug–target interactions in preclinical research. While novel structures and designs are commonly explored in probe development, the clinical translation of small-molecule probes remains limited, primarily due to safety and regulatory considerations. Recent synergistic developments – interfacing novel chemical probes with complementary analytical technologies – have introduced and expedited diverse biomedical opportunities to molecularly characterize targeted drug interactions directly in the human body or through accessible clinical specimens (e.g., blood and ascites fluid). These integrated developments thus offer unprecedented opportunities for drug development, disease diagnostics and treatment monitoring. In this review, we discuss recent advances in the structure and design of small-molecule probes with novel functionalities and the integrated development with imaging, proteomics and other emerging technologies. We further highlight recent applications of integrated small-molecule technologies for the molecular analysis of drug–target interactions, including translational applications and emerging opportunities for whole-body imaging, tissue-based measurement and blood-based analysis.

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A General One-Step Synthesis of Alkanethiyl-Stabilized Gold Nanoparticles with Control over Core Size and Monolayer Functionality

Stefan Borsley, William Edwards, Ioulia K. Mati, Guillaume Poss, Marta Diez-Castellnou, Nicolas Marro, and Euan R. Kay*

Cite This: Chem. Mater. 2023, 35, 6168−6177

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ABSTRACT: In spite of widespread interest in the unique size-dependent properties and consequent applications of gold nanoparticles (AuNPs), synthetic protocols that reliably allow for independent tuning of surface chemistry and core size, the two critical determinants of AuNP properties, remain limited. Often, core size is inherently affected by the ligand structure in an unpredictable fashion. Functionalized ligands are commonly introduced using postsynthesis exchange procedures, which can be inefficient and operationally delicate. Here, we report a one step protocol for preparing monolayer-stabilized AuNPs that is compatible with a wide range of ligand functional groups and also allows for the systematic control of core size. In a single-phase reaction using the mild reducing agent *tert*-butylamine borane, AuNPs that are compatible with solvents spanning a wide range of polarities from toluene to water can be produced without damaging reactive chemical functionalities within the small-molecule surface-stabilizing ligands. We demonstrate that the rate of reduction, which is easily controlled by adjusting the period over which the reducing agent is added, is a simple parameter that can be used irrespective of the ligand structure to adjust the core size of AuNPs without broadening the size distribution. Core sizes in the range of 2−10 nm can thus be generated. The upper size limit appears to be determined by the nature of each specific ligand/solvent pairing. This protocol produces high quality, functionally sophisticated nanoparticles in a single step. By combining the ability to vary size-related nanoparticle properties with the option to incorporate reactive functional groups at the nanoparticle−solvent interface, it is possible to generate chemically reactive colloidal building blocks from which more complex nanoparticle-based devices and materials may subsequently be constructed.

INTRODUCTION

Metal nanoparticles (NPs) have generated much excitement as a result of their distinct properties, which are dependent on the core material, size, and shape, making them of interest for an ever-expanding range of applications.[1−3] Commonly, the inorganic core is stabilized by a surface-bound monolayer of molecular ligands, as exemplified by the archetypal alkanethiyl-stabilized gold nanoparticle (AuNP).[4,5] Defining the interface between the nanoparticle core and surrounding matrix, the ligand shell is also a critical determinant of numerous properties, including solvent compatibility, catalytic activity, nanoparticle−molecule interactions, and optical and electronic behavior.[6−10] Furthermore, surface-bound ligands that incorporate reactive sites provide a handle for conjugating additive functionality or appending nanoparticles to other components in postsynthesis manipulations.[11−14] Consequently, size-controlled synthesis of nanoparticle populations with narrow size distributions is critical for tuning nanoparticle properties and is, therefore, a long-standing central challenge in nanochemistry. However, the majority of methods focus only on controlling features of the metallic core, typically stabilized by nonfunctionalized ligands that are inadequate for many applications.[15] Synthesis strategies that easily allow for independent tuning of both the core and the ligand parameters will accelerate the systematic and efficient development of nanoparticle based applications.

Since the first practical synthesis of alkanethiyl-stabilized AuNPs by Brust and Schiffrin,[16] there have been several important advances in the synthetic methodology.[15,17,18] However, size control remains a significant challenge,

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Anionic polysaccharides for stabilization and sustained release of antimicrobial peptides

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ABSTRACT

Chemical and enzymatic *in vivo* degradation of antimicrobial peptides represents a major challenge for their therapeutic use to treat bacterial infections. In this work, anionic polysaccharides were investigated for their ability to increase the chemical stability and achieve sustained release of such peptides. The investigated formulations comprised a combination of antimicrobial peptides (vancomycin (VAN) and daptomycin (DAP)) and anionic polysaccharides (xanthan gum (XA), hyaluronic acid (HA), propylene glycol alginate (PGA) and alginic acid (ALG)). VAN dissolved in buffer of pH 7.4 and incubated at 37 °C showed first order degradation kinetics with a reaction rate constant k_{obs} of 5.5×10^{-2} day^{-1} corresponding with a half-life of 13.9 days. However, once VAN was present in a XA, HA or PGA-based hydrogel, k_{obs} decreased to $(2.1–2.3) \times 10^{-2}$ day^{-1} while k_{obs} was not affected in an alginate hydrogel and a dextran solution (5.4×10^{-2} and 4.4×10^{-2} day^{-1}). Under the same conditions, XA and PGA also effectively decreased k_{obs} for DAP (5.6×10^{-2} day^{-1}), whereas ALG had no effect and HA even increased the degradation rate. These results demonstrate that the investigated polysaccharides (except ALG for both peptides and HA for DAP) slowed down the degradation of VAN and DAP. DSC analysis was used to investigate on polysaccharide ability to bind water molecules. Rheological analysis highlighted that the polysaccharides containing VAN displayed an increase in G' of their formulations, pointing that the peptides interaction act as crosslinker of the polymer chains. The obtained results suggest that the mechanism of stabilization of VAN and DAP against hydrolytic degradation is conferred by electrostatic interactions between the ionizable amine groups of the drugs and the anionic carboxylate groups of the polysaccharides. This, in turn, results in a close proximity of the drugs to the polysaccharide chain, where the water molecules have a lower mobility and, therefore, a lower thermodynamic activity.

1. Introduction

Over recent decades, biotherapeutic peptides have been thoroughly studied as a new class of drugs for the treatment of a variety of chronic and life-threatening diseases. Because of their short half-life, high doses have to be administered to reach therapeutic drug concentrations at the target site. These high doses, however, result in high initial blood concentrations which in turn are associated with side effects and systemic

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[1] In Memoriam of our valued colleague and friend Stefania Scuri who contributed to this manuscript and tragically passed away.

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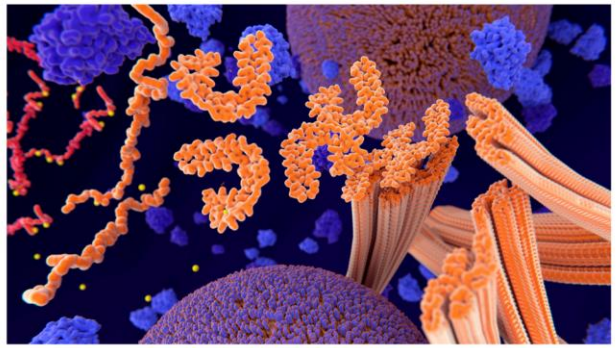
A rare mutation helped one man stave off Alzheimer's for decades

It's the second such case ever to be reported



Aggregations of proteins called tau tangles (orange clumps in this illustration of a brain cell) are one of the major signs of Alzheimer's disease.
JUAN GAERTNER/SCIENCE PHOTO LIBRARY/GETTY IMAGES PLUS

By Simon Makin

MAY 15, 2023 AT 11:00 AM

A rare genetic mutation never seen before protected a man with an inherited form of Alzheimer's from developing the disease for decades.

He is the second person found to have such protection, following a report in 2019 of a woman with a different mutation (*SN: 1/26/20*). Both mutations may have staved off the disease for years by acting in similar ways in the brain, an insight that could lead to new treatments for all forms of Alzheimer's, scientists report May 15 in *Nature Medicine*.

nature medicine

Article https://doi.org/10.1038/s41591-023-02318-3

Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man

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We characterized the world's second case with ascertained extreme resilience to autosomal dominant Alzheimer's disease (ADAD). Side-by-side comparisons of this male case and the previously reported female case with ADAD homozygote for the *APOE3* Christchurch (*APOECh*) variant allowed us to discern common features. The male remained cognitively intact until 67 years of age despite carrying a *PSEN1*-E280A mutation. Like the *APOECh* carrier, he had extremely elevated amyloid plaque burden and limited entorhinal Tau tangle burden. He did not carry the *APOECh* variant but was heterozygous for a rare variant in *RELN* (H3447R, termed *COLBOS* after the Colombia–Boston biomarker research study), a ligand that like apolipoprotein E binds to the VLDLr and APOEr2 receptors. *RELN-COLBOS* is a gain-of-function variant showing stronger ability to activate its canonical protein target Dab1 and reduce human Tau phosphorylation in a knockin mouse. A genetic variant in a case protected from ADAD suggests a role for *RELN* signaling in resilience to dementia.

We have characterized about 1,200 individuals carrying the presenilin 1 (*PSEN1*) E280A mutation from the world's largest known kindred with autosomal dominant Alzheimer's disease (ADAD). Carriers of the *PSEN1*-E280A mutation develop mild cognitive impairment (MCI) by the median age of 44 years (95% confidence interval (CI) = 43–45) and dementia by 49 years (95% CI = 49–50)[1], with rare exceptions[2]. We previously reported a female carrying the *PSEN1*-E280A mutation with two copies of the *APOE3* Christchurch (*APOECh*) (R136S) gene variant

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Nanoparticle

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A **nanoparticle** or **ultrafine particle** is usually defined as a particle of matter that is between 1 and 100 nanometres (nm) in diameter.[1][2] The term is sometimes used for larger particles, up to 500 nm,[*citation needed*] or fibers and tubes that are less than 100 nm in only two directions.[3] At the lowest range, metal particles smaller than 1 nm are usually called atom clusters instead.

Nanoparticles are usually distinguished from microparticles (1-1000 μm), "fine particles" (sized between 100 and 2500 nm), and "coarse particles" (ranging from 2500 to 10,000 nm), because their smaller size drives very different physical or chemical properties, like colloidal properties and ultrafast optical effects[4] or electric properties.

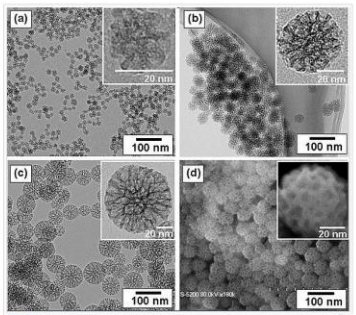
Being more subject to the Brownian motion, they usually do not sediment, like colloidal particles that conversely are usually understood to range from 1 to 1000 nm.

Being much smaller than the wavelengths of visible light (400-700 nm), nanoparticles cannot be seen with ordinary optical microscopes, requiring the use of electron microscopes or microscopes with laser. For the same reason, dispersions of nanoparticles in transparent media can be transparent,[5] whereas suspensions of larger particles usually scatter some or all visible light incident on them. Nanoparticles also easily pass through common filters, such as common ceramic candles,[6] so that separation from liquids requires special nanofiltration techniques.

The properties of nanoparticles often differ markedly from those of larger particles of the same substance. Since the typical diameter of an atom is between 0.15 and 0.6 nm, a large fraction of the nanoparticle's material lies within a few atomic diameters of its surface. Therefore, the properties of that surface layer may dominate over those of the bulk material. This effect is particularly strong for nanoparticles dispersed in a medium of different composition since the interactions between the two materials at their interface also becomes significant.[7]

Nanoparticles occur widely in nature and are objects of study in many sciences such as chemistry, physics, geology, and biology. Being at the transition between bulk materials and atomic or molecular structures, they often exhibit phenomena that are not observed at either scale. They are an important component of atmospheric pollution, and key ingredients in many industrialized products such as paints, plastics, metals, ceramics, and magnetic products. The production of nanoparticles with specific properties is a branch of nanotechnology.

In general, the small size of nanoparticles leads to a lower concentration of point defects compared to their bulk counterparts,[8] but they do support a variety of dislocations that can be visualized using high-resolution electron microscopes.[9] However, nanoparticles exhibit different dislocation mechanics, which, together with their unique surface structures, results in mechanical properties that are different from the bulk material.[10][11][12]



TEM (a, b, and c) images of prepared mesoporous silica nanoparticles with mean outer diameter: (a) 20nm, (b) 45nm, and (c) 80nm. SEM (d) image corresponding to (b). The insets are a high magnification of mesoporous silica particle.

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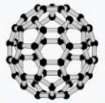

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Gene therapy could hold the cure to many of the world's most devastating diseases. Read this blog to learn how Organ-Chips could be key to unlocking this potential.

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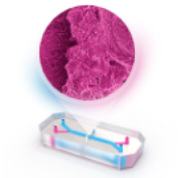
Modeling Inflammation-Specific Immune Cell Recruitment in the Colon Intestine-Chip



Abstract

Inflammatory bowel disease (IBD) is a complex pathology with a large, rapidly growing, unmet medical need. The Colon Intestine-Chip was previously developed as a primary human vascularized model of the intestinal barrier that recapitulates physiologic cell composition, morphology, and barrier function. The current application models the progression of IBD driven by immune cells. Thus, a 'priming' cytokine/chemokine stimulus relevant to the initiation phase of IBD was introduced to the Colon Intestine-Chip, followed by perfusion of PBMCs into the vascular channel. This led to the selective attachment and recruitment of gut-specific immune cells into the epithelium, where they engaged in effector functions, including the release of IBD-associated cytokines (e.g., IFNγ, IL-22) and the hallmark leaky gut feature. Co-treatment with clinically relevant IBD therapeutics reduced PBMC recruitment and protected the epithelium from downstream cytokine and permeability responses. Therefore, this model may prove to be uniquely effective at enabling development of novel anti-inflammatory therapeutics for human intestinal diseases.

Key Highlights

- The Colon Intestine-Chip provides a physiological platform for investigating pathophysiology of inflammatory diseases affecting the intestinal barrier.
- This model can be applied to study inflammation-specific immune recruitment from vasculature into epithelial tissue and subsequent downstream effects.
- Treatment with clinically relevant IBD therapeutics reduces PBMC recruitment and protects the epithelium from downstream cytokine and permeability responses.
- This model provides the most complete picture of human IBD pathogenesis and a more human-relevant platform for drug candidate efficacy and mechanism-of-action studies.

Introduction

IBD is a rapidly growing disease area, particularly across Asia and Africa, with global prevalence increasing from 3.7M in 1990 to 6.8M in 2017.[1,2] A substantial portion of the affected population (40-50%) fails to respond to existing treatments; for those that do respond, 65-80% either fail to enter full remission or lose therapeutic benefit over time.[3] Significant research challenges remain, including the identification of mechanisms that translate to druggable targets.[4] Overall, there is an urgent need for more effective therapeutics for IBD and other diseases involving leaky gut pathologies.

Typically, research has relied on two IBD models: 1. Animal models have provided insights into disease pathogenesis; however, most drugs developed using animals fail to translate to human response due to species differences in immune responses. 2. Conventional *in vitro* models only recapitulate a narrow window of disease features, often using non-human cell sources. Thus, developing effective therapeutics requires advanced, physiologic, immunologically complex, human-relevant models. With the Colon Intestine-Chip, the essential pathways of IBD can be modeled *in vitro* in a human-relevant manner. IBD progression is mediated by uncontrolled recruitment and activation of intestinal immune cells. Early in IBD, tissue insults induce production of pro-inflammatory cytokines and chemokines, which then elicit selective recruitment of immune cells from blood circulation into the intestinal microenvironment. This results in immune-cell-driven, pro-inflammatory cascades that induce cytokine-mediated epithelial leakage. This, in turn, stimulates further immune cell accumulation and activation, driving chronic intestinal inflammation. The model described herein was designed to recapitulate complete human IBD pathogenesis for the first time, thereby enabling the development of new therapeutics.

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pH Meter Guide

pH is a measurement of acidity or alkalinity in a food using a numerical scale from 1 to 14. A pH below 7 is acidic, a pH of 7 is neutral, and a pH value above 7 is basic or alkaline. Monitoring pH levels during food processing is an important step in the production of some food since pH values affect microbial growth.

Acidity and pH

The acidity of food can be determined by measuring its pH value. To preserve food using acidity alone, it needs to have an equilibrium pH value of 4.6 or lower. Equilibrium pH is the pH of a food after all components of the food have achieved the same acidity. Foods with a pH greater than 4.6 are considered low acid foods.

Foods with a pH less than 4.6 can be called acid foods. An acidified food is a low acid food with acidic ingredients added to it to lower the pH (e.g., vinegar).

pH and micro-organisms

pH affects the growth of micro-organisms. At about pH 7, most pathogenic bacteria grow well. At pH 4.6 or below, most pathogenic bacteria cannot grow and *Clostridium botulinum* will not produce toxin. However, some spoilage micro-organisms can grow in low pH foods.

What is a pH meter?

A pH meter is an electronic device used to measure the pH of a solution or food. It has an electrode (measuring probe) connected to an electronic meter that displays the pH reading.

How to select a pH meter

A pH meter should be easy to use, offer reliable results and have a long life span. Things to consider include:

- **Accuracy:** It is the most important factor in measuring pH. It is recommended to use a pH meter with an accuracy of at least ±0.02 units.
- **Electrode:** It is the part of the pH meter immersed in the sample. Select an electrode suitable for the food you are testing. For instance, some electrodes have spear tips that are more suitable for measuring the pH of semi-solid food.
- **Use:** Bench top models are suitable for laboratory use. If the pH meter will be taken into the plant, then a handheld model may be more appropriate.

Temperature

Temperature can affect pH readings. To get an accurate reading, the pH meter must be calibrated at the same temperature as the samples being tested. Usually, pH meters are used and calibrated at room temperature.

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(54) **Use of emulsions for intra- and periocular injection**

Verwendung von Emulsionen zur intra- und perioculären Injection

Utilisation des émulsions pour injection intra- et périoculaire.

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(56) References cited:

EP-A- 0 521 799 **EP-A- 1 020 194** **WO-A-02/09667** **WO-A-93/18852** **WO-A-94/05298** **WO-A-03/053405** **US-A- 5 632 984**

- **KLANG S H ET AL: "PHYSICOCHEMICAL CHARACTERIAZATION AND ACUTE TOXICITY EVALUATION OF A POSITIVELY-CHARGED SUBMICRON EMULSION VEHICLE" JOURNAL OF PHARMACY AND PHARMACOLOGY, LONDON, GB, vol. 46, no. 12, December 1994 (1994-12), pages 986-993, XP008005426 ISSN: 0022-3573**
- **KLANG S ET AL: "INFLUENCE OF EMULSION DROPLET SURFACE CHARGE ON INDOMETHACIN OCULAR TISSUE DISTRIBUTION" PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, NEW YORK, NY, US, vol. 5, no. 4, 2000, pages 521-532, XP008005503 ISSN: 1083-7450**
- **ABDULRAZIK M ET AL: "OCULAR DELIVERY OF CYCLOSPORIN A II. EFFECT OF SUBMICRON EMULSION'S SURFACE CHARGE ON OCULAR DISTRIBUTION OF TOPICAL CYCLOSPORIN A" STP PHARMA SCIENCES, PARIS, FR, vol. 11, no. 6, 2001, pages 427-432, XP008033036 ISSN: 1157-1489**

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EP 1 611 879 B1

US011338118B2

(12) **United States Patent** **Imran**

(10) **Patent No.: US 11,338,118 B2**

(45) **Date of Patent: May 24, 2022**

(54) **SWALLOWABLE DRUG DELIVERY DEVICE AND METHODS OF DRUG DELIVERY**

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(72) Inventor: **Mir Imran**, Los Altos Hills, CA (US)

(73) Assignee: **RANI THERAPEUTICS, LLC**, San Jose, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 296 days.

(21) Appl. No.: **16/782,959**

(22) Filed: **Feb. 5, 2020**

(65) **Prior Publication Data**

US 2020/0171287 A1 Jun. 4, 2020

Related U.S. Application Data

(60) Continuation of application No. 16/275,586, filed on Feb. 14, 2019, now Pat. No. 10,603,475, which is a (Continued)

(51) **Int. Cl.**
A61M 31/00 (2006.01)
A61K 31/155 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61M 31/002*** (2013.01); ***A61K 9/0065*** (2013.01); ***A61K 9/48*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC A61M 31/002; A61M 2005/14284; A61M 2210/106; A61K 9/0065; A61K 9/48; A61K 9/4808
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,788,322 A 1/1974 Michaels
4,055,641 A 10/1977 Benson et al.
(Continued)

FOREIGN PATENT DOCUMENTS

CN 2860501 Y 1/2007
CN 101330940 A 12/2008
(Continued)

OTHER PUBLICATIONS

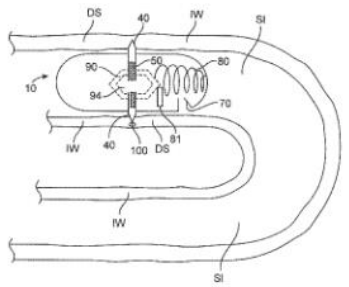
Co-pending U.S. Appl. No. 16/828,736, filed Mar. 24, 2020.
(Continued)

Primary Examiner — Bradley J Osinski
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Embodiments of the invention provide swallowable devices, preparations and methods for delivering drugs and other therapeutic agents within the GI tract. Some embodiments provide a swallowable device such as a capsule for delivering drugs into the intestinal wall or other GI lumen. The device comprises a capsule sized to be swallowed and pass through the intestinal tract. The capsule can include at least one guide tube, one or more tissue penetrating members positioned in the guide tube, a delivery member, an actuating mechanism and a release element. The release element degrades upon exposure to various conditions in the intestine so as to release and actuate the actuating mechanism. Embodiments of the invention are particularly useful for the delivery of drugs which are poorly absorbed, tolerated and/or degraded within the GI tract.

22 Claims, 45 Drawing Sheets



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9e rang

2019-2022

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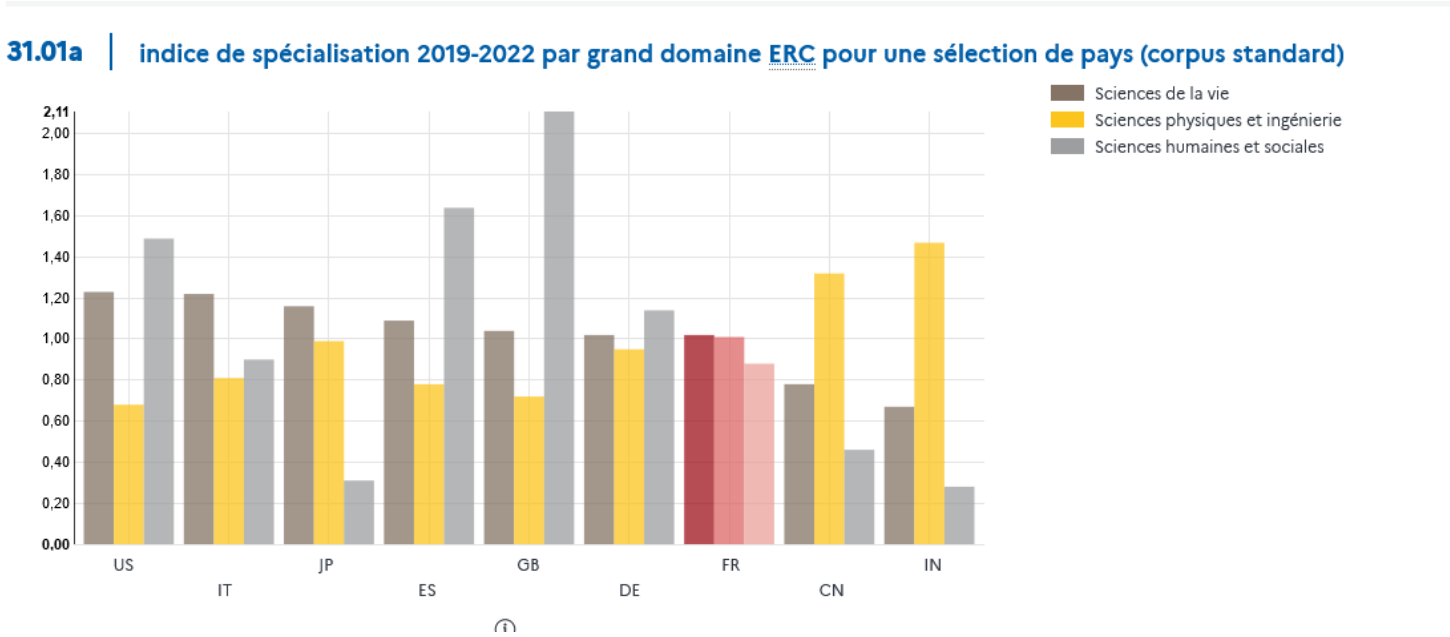
2019-2022



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When is the decision made to write a scientific publication?

Originality and Contribution	Significance	Comprehensiveness	Validity and Reproducibility	Ethics and Integrity
▪ Have these findings been reported before? ▪ How does this research add to existing knowledge?	▪ How does this research address a key question? ▪ What impact could these findings have?	▪ Does the research cover all relevant aspects? ▪ Are there any gaps in the analysis?	▪ Are the experiments well-designed and unbiased? ▪ Can other researchers replicate the methods?	▪ Are all sources properly cited? ▪ Is the data accurately presented?

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What journals should you publish in?

Relevance to Your Field	Quality and Reputation	Ethical Standards	Indexing & Visibility	Citations and Impact Factor
▪ Your research reaches an audience interested in your field, increasing its impact and relevance	▪ Adds credibility to your work	▪ Reinforces the integrity of your research	▪ Other researchers find and cite your work ▪ H-index	▪ Rough measure of a journal influence and recognition in the academic community ▪ **Not the sole indicator of quality**

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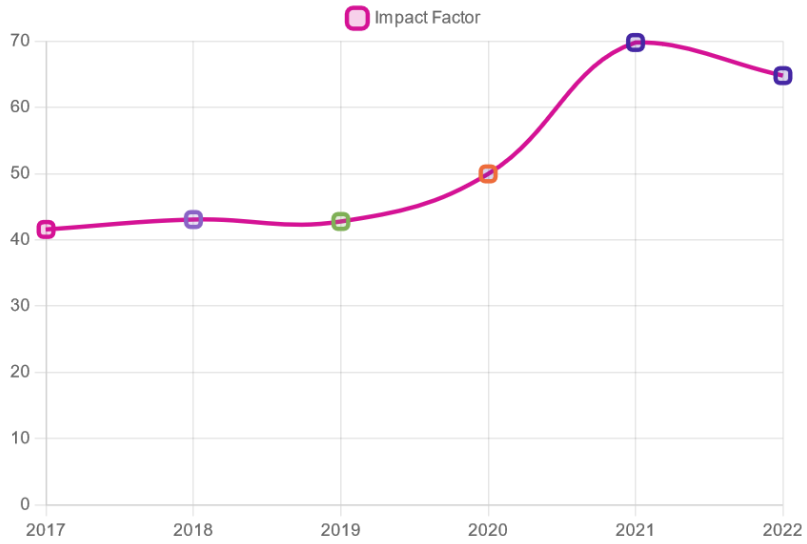
nature

Citation Impact 2023

- Journal Impact Factor: 50.5
- 5-year Journal Impact Factor: 54.4

$$\text{IF} = \frac{\text{Number of citations in } y^{\text{th}} \text{ year}}{\text{Sum of publications in last 2 years } (y\text{-}1,\ y\text{-}2)}$$



64.8

Impact Factor

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Beware the impact factor

The journal impact factor is a good predictor of the quality of journals as measured by citations to primary research articles. It is, however, a poor indicator of citations to specific papers or of the future performance of individual researchers.

When it comes to scientific measures, the journal impact factor wins both in terms of broadest use and as the most loathed metric[1,2]. Indeed, the fact that it is simple to understand — it is roughly the average number of citations that primary research papers published in two consecutive years gather in the following year — makes it all too easy to point out its shortcomings: the metric also includes citations to non-primary content (such as reviews and news articles); for many fields, citations accumulate slowly and thus the two-year time window seems too short; and the average number of citations per paper can be skewed by a few highly cited ones[3], of which high-impact journals have a big share. Many feel that these limitations favour highly selective and multidisciplinary journals disproportionally.

Here we argue that these limitations are irrelevant. Figure 1 shows that, for a sample of 100 journals across the spectrum of science and engineering, the 2011 impact factor correlates well with the five-year median of citations to primary research papers published in 2008–2012. It is important to stress that the values for the median — which corresponds to the minimum number of citations received by half of the papers, and thus is robust to outliers and variations in the shape of the distribution — do not include citations to non-primary content and have a time window of five years.

That citation averages (such as the impact factor) and medians correlate is not surprising if one considers that the shape of the citation distributions may be comparable across journals, as the similarities between the usual two-year and the less-known five-year impact factors suggests[4]. What is perhaps unexpected is the robustness of the impact factor as a predictive metric: citations to non-primary content and the apparently too short two-year time window have little effect on the overall correlation. Still, it is interesting to note that the largest deviations from the linear fit in Fig. 1 correspond to medical journals, some of which produce a disproportionate amount of non-primary content (such as *The Lancet and The Journal of the American Medical Association*) or to journals that have significantly altered the yearly amount of primary content during the five-year time frame for which the median is calculated.

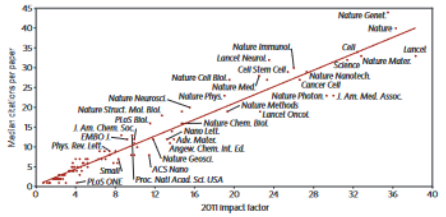

Figure 1 | A journal's impact factor is a good predictor of its five-year median of citations to primary research articles. The data and linear fit ($r^2 = 0.94$) correspond to a sample of 100 journals launched before 2008. The five-year median values are of citations (as of 5 January 2013) to research papers (that is, excluding reviews, news, editorial material and other non-primary research articles) published in 2008–2012. The specific median values and slope of the linear fit (here 1.04) depend on the citation time window (here 1 January 2008 to 5 January 2013), impact-factor year and data source (here Thomson Reuters Web of Science). Journals included in the sample span the physical and chemical sciences, the biological and medical sciences, the earth and environmental sciences, and engineering.

As a case in point, the median number of citations for *PLoS ONE* is 1 whereas its 2011 impact factor is 4.1, largely because since 2008 it has increased its output more than six-fold[5] (from less than 3,000 papers in 2008 to about 19,000 in 2012). The impact factor, being a lagging indicator with a narrower time window, has yet to reflect this.

It is therefore clear that but for outliers[6,7] the impact factor is an appropriate measure of journal quality according to citations. And it is also beyond question that the impact factor does not generally correlate to the performance of individual researchers or to citations to individual papers[3,8,9]. As with any statistical measure, it is unsafe to use it as a proxy for an unrepresentative subset of the original sample. It would thus be unwise, for instance, to rate scientists on the basis of the total number of papers weighted according to the impact factor of the journal where they have been published. A simple exercise proves the point: pick a few scientists and rank the papers they published five years ago in decreasing order of citations alongside the impact factor of the corresponding journal in that year. The odds are that, if there is any correlation at all, this is weak or the outliers are plentiful.

As Fig. 1 shows, half of the papers published by *Nature Materials* in the past five years have received more citations than at least half the papers published in most other journals (that is, any journal with a lower impact factor). The median and its predictor the impact factor are therefore quality signals that are valid for comparisons between journals publishing on similar scientific topics. Yet beware of those who use them instead of article-level metrics[10] when assessing a small subgroup of papers or authors. Impact factors should have no place in grant-giving, tenure or appointment committees.

References
1. http://occamstypewriter.org/scurry/2012/08/13/sick-of-impact-factors
2. Cameron, B. D. *Portal Libraries Acad.* **5**, 105–125 (2005).
3. *Nature Mater.* **10**, 645 (2011).
4. Campanario, J. M. *Scientometrics* **87**, 189–204 (2011).
5. *Nature Mater.* **11**, 353 (2012).
6. Thomson Reuters, http://go.nature.com/yPnnfb
7. Campanario, J. M. *J. Am. Soc. Inf. Sci. Technol.* **62**, 230–235 (2011).
8. Rostami-Hodjegan, A. & Tucker, G. T. *Br. J. Clin. Pharmacol.* **51**, 111–117 (2001).
9. Epstein, R. *J. J. Invest. Med.* **52**, 531–536 (2004).
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Sick of Impact Factors

Posted on August 13, 2012 by Stephen

I am sick of impact factors and so is science.

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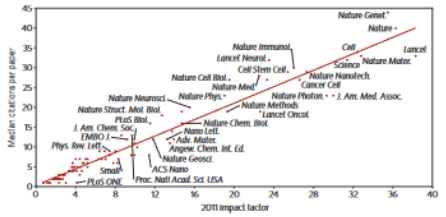

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Injectable Adhesive Self-Healing Multiple-Dynamic-Bond Crosslinked Hydrogel with Photothermal Antibacterial Activity for Infected Wound Healing

Huilong Guo, Shan Huang*, Anding Xu*, and Wei Xue*

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Publication Date: March 10, 2022
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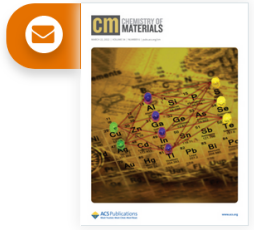

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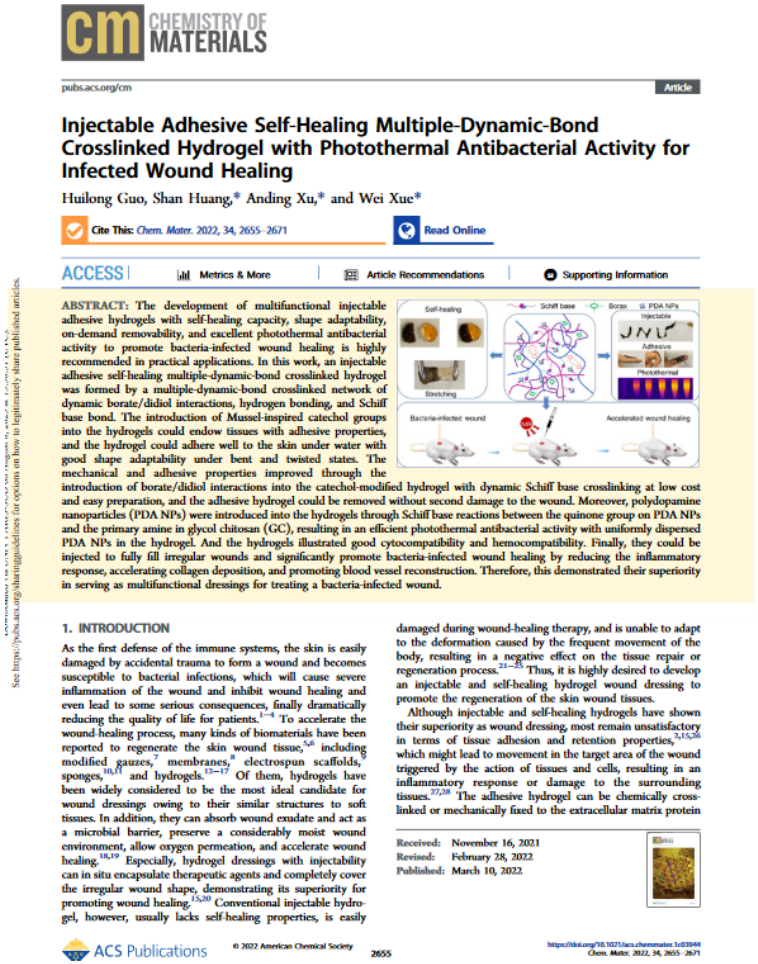

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Injectable Adhesive Self-Healing Multiple-Dynamic-Bond Crosslinked Hydrogel with Photothermal Antibacterial Activity for Infected Wound Healing

Huilong Guo, Shan Huang,* Anding Xu,* and Wei Xue*

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ABSTRACT: The development of multifunctional injectable adhesive hydrogels with self-healing capacity, shape adaptability, on-demand removability, and excellent photothermal antibacterial activity to promote bacteria-infected wound healing is highly recommended in practical applications. In this work, an injectable adhesive self-healing multiple-dynamic-bond crosslinked hydrogel was formed by a multiple-dynamic-bond crosslinked network of dynamic borate/didiol interactions, hydrogen bonding, and Schiff base bond. The introduction of Mussel-inspired catechol groups into the hydrogels could endow tissues with adhesive properties, and the hydrogel could adhere well to the skin under water with good shape adaptability under bent and twisted states. The mechanical and adhesive properties improved through the introduction of borate/didiol interactions into the catechol-modified hydrogel with dynamic Schiff base crosslinking at low cost and easy preparation, and the adhesive hydrogel could be removed without second damage to the wound. Moreover, polydopamine nanoparticles (PDA NPs) were introduced into the hydrogels through Schiff base reactions between the quinone group on PDA NPs and the primary amine in glycol chitosan (GC), resulting in an efficient photothermal antibacterial activity with uniformly dispersed PDA NPs in the hydrogel. And the hydrogels illustrated good cytocompatibility and hemocompatibility. Finally, they could be injected to fully fill irregular wounds and significantly promote bacteria-infected wound healing by reducing the inflammatory response, accelerating collagen deposition, and promoting blood vessel reconstruction. Therefore, this demonstrated their superiority in serving as multifunctional dressings for treating a bacteria-infected wound.

1. INTRODUCTION

As the first defense of the immune systems, the skin is easily damaged by accidental trauma to form a wound and becomes susceptible to bacterial infections, which will cause severe inflammation of the wound and inhibit wound healing and even lead to some serious consequences, finally dramatically reducing the quality of life for patients.[1−4] To accelerate the wound-healing process, many kinds of biomaterials have been reported to regenerate the skin wound tissue,[5,6] including modified gauzes,[7] membranes,[8] electrospun scaffolds,[9] sponges,[10,11] and hydrogels.[12−17] Of them, hydrogels have been widely considered to be the most ideal candidate for wound dressings owing to their similar structures to soft tissues. In addition, they can absorb wound exudate and act as a microbial barrier, preserve a considerably moist wound environment, allow oxygen permeation, and accelerate wound healing.[18,19] Especially, hydrogel dressings with injectability can in situ encapsulate therapeutic agents and completely cover the irregular wound shape, demonstrating its superiority for promoting wound healing.[15,20] Conventional injectable hydrogel, however, usually lacks self-healing properties, is easily damaged during wound-healing therapy, and is unable to adapt to the deformation caused by the frequent movement of the body, resulting in a negative effect on the tissue repair or regeneration process.[21−23] Thus, it is highly desired to develop an injectable and self-healing hydrogel wound dressing to promote the regeneration of the skin wound tissues.

Although injectable and self-healing hydrogels have shown their superiority as wound dressing, most remain unsatisfactory in terms of tissue adhesion and retention properties,[3,15,24] which might lead to movement in the target area of the wound triggered by the action of tissues and cells, resulting in an inflammatory response or damage to the surrounding tissues.[25,26] The adhesive hydrogel can be chemically cross-linked or mechanically fixed to the extracellular matrix protein

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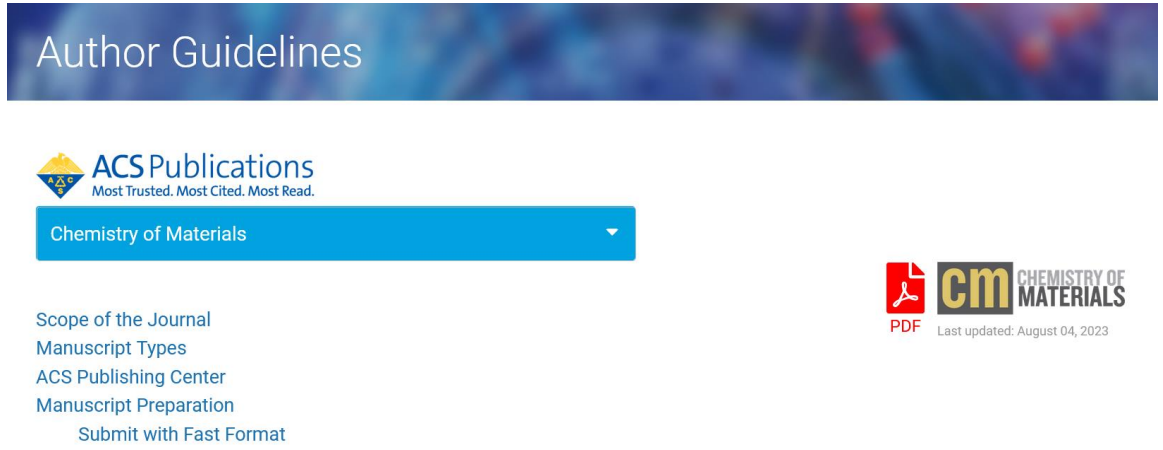

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- Introduction
- Experimental Section
- Results
- Discussion
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- Acknowledgements
- Supporting Information description
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Injectable Adhesive Self-Healing Multiple-Dynamic-Bond Crosslinked Hydrogel with Photothermal Antibacterial Activity for Infected Wound Healing

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Avoid Being Too Short

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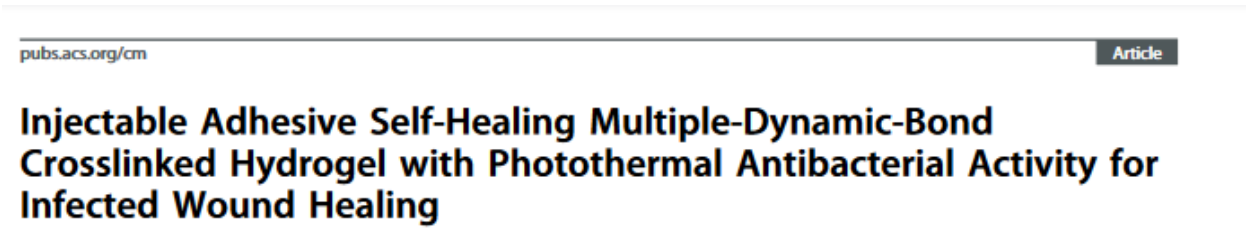
Self-healing, injectable, cross-linked hydrogel with multiple dynamic bonds, using the photothermal mechanism to exhibit effective antibacterial activity to facilitate enhanced healing of wounds infected by bacterial pathogens.

Incorporate Important Keywords



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The Funnel Principle

- Introduce the problem
- Explain why this topic matters
- Mention the hypotheses or research questions explored by your article
- Clearly state the objectives of your article
- Provide an overview of the methodological approach
- Mention a few key results

Communicating scientific results

Write a scientific article: the introduction

The Funnel Principle

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The details

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Clearly describe the steps, conditions and variables involved in your experiments

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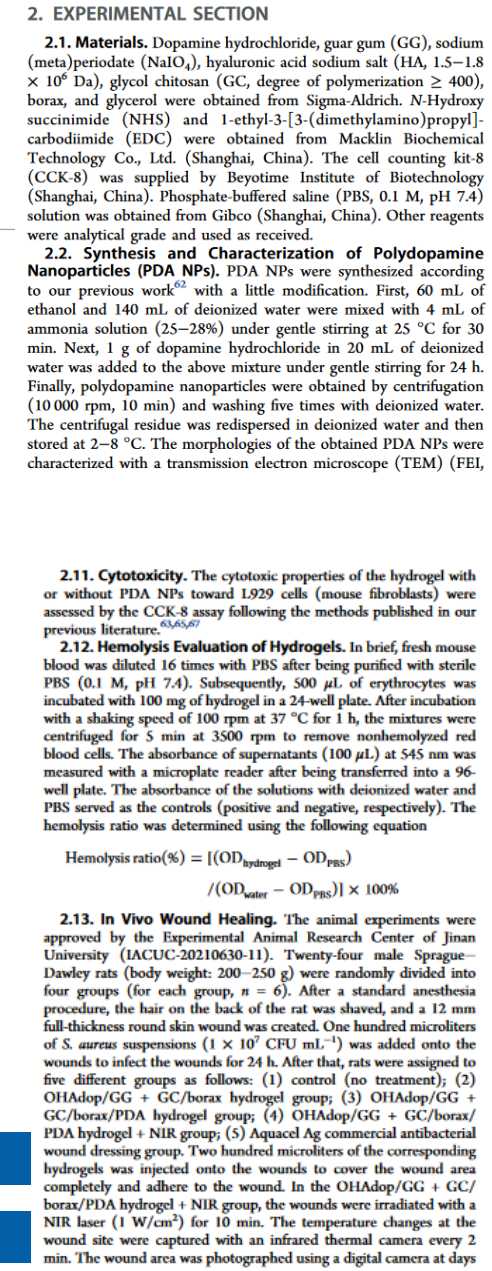

2. EXPERIMENTAL SECTION

2.1. Materials. Dopamine hydrochloride, guar gum (GG), sodium (meta)periodate ($NaIO_4$), hyaluronic acid sodium salt (HA, 1.5−1.8 × 10^6 Da), glycol chitosan (GC, degree of polymerization ≥ 400), borax, and glycerol were obtained from Sigma-Aldrich. *N*-Hydroxy succinimide (NHS) and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (EDC) were obtained from Macklin Biochemical Technology Co., Ltd. (Shanghai, China). The cell counting kit-8 (CCK-8) was supplied by Beyotime Institute of Biotechnology (Shanghai, China). Phosphate-buffered saline (PBS, 0.1 M, pH 7.4) solution was obtained from Gibco (Shanghai, China). Other reagents were analytical grade and used as received.

2.2. Synthesis and Characterization of Polydopamine Nanoparticles (PDA NPs). PDA NPs were synthesized according to our previous work[62] with a little modification. First, 60 mL of ethanol and 140 mL of deionized water were mixed with 4 mL of ammonia solution (25−28%) under gentle stirring at 25 °C for 30 min. Next, 1 g of dopamine hydrochloride in 20 mL of deionized water was added to the above mixture under gentle stirring for 24 h. Finally, polydopamine nanoparticles were obtained by centrifugation (10 000 rpm, 10 min) and washing five times with deionized water. The centrifugal residue was redispersed in deionized water and then stored at 2−8 °C. The morphologies of the obtained PDA NPs were characterized with a transmission electron microscope (TEM) (FEI,

2.11. Cytotoxicity. The cytotoxic properties of the hydrogel with or without PDA NPs toward L929 cells (mouse fibroblasts) were assessed by the CCK-8 assay following the methods published in our previous literature.[63,65,67]

2.12. Hemolysis Evaluation of Hydrogels. In brief, fresh mouse blood was diluted 16 times with PBS after being purified with sterile PBS (0.1 M, pH 7.4). Subsequently, 500 μL of erythrocytes was incubated with 100 mg of hydrogel in a 24-well plate. After incubation with a shaking speed of 100 rpm at 37 °C for 1 h, the mixtures were centrifuged for 5 min at 3500 rpm to remove nonhemolyzed red blood cells. The absorbance of supernatants (100 μL) at 545 nm was measured with a microplate reader after being transferred into a 96-well plate. The absorbance of the solutions with deionized water and PBS served as the controls (positive and negative, respectively). The hemolysis ratio was determined using the following equation

$$\text{Hemolysis ratio}(\%) = [(OD_{\text{hydrogel}} - OD_{\text{PBS}}) / (OD_{\text{water}} - OD_{\text{PBS}})] \times 100\%$$

2.13. In Vivo Wound Healing. The animal experiments were approved by the Experimental Animal Research Center of Jinan University (IACUC-20210630-11). Twenty-four male Sprague−Dawley rats (body weight: 200−250 g) were randomly divided into four groups (for each group, $n = 6$). After a standard anesthesia procedure, the hair on the back of the rat was shaved, and a 12 mm full-thickness round skin wound was created. One hundred microliters of *S. aureus* suspensions (1 × 10^7 CFU mL^{-1}) was added onto the wounds to infect the wounds for 24 h. After that, rats were assigned to five different groups as follows: (1) control (no treatment); (2) OHAdop/GG + GC/borax hydrogel group; (3) OHAdop/GG + GC/borax/PDA hydrogel group; (4) OHAdop/GG + GC/borax/PDA hydrogel + NIR group; (5) Aquacel Ag commercial antibacterial wound dressing group. Two hundred microliters of the corresponding hydrogels was injected onto the wounds to cover the wound area completely and adhere to the wound. In the OHAdop/GG + GC/borax/PDA hydrogel + NIR group, the wounds were irradiated with a NIR laser (1 W/cm^2) for 10 min. The temperature changes at the wound site were captured with an infrared thermal camera every 2 min. The wound area was photographed using a digital camera at days

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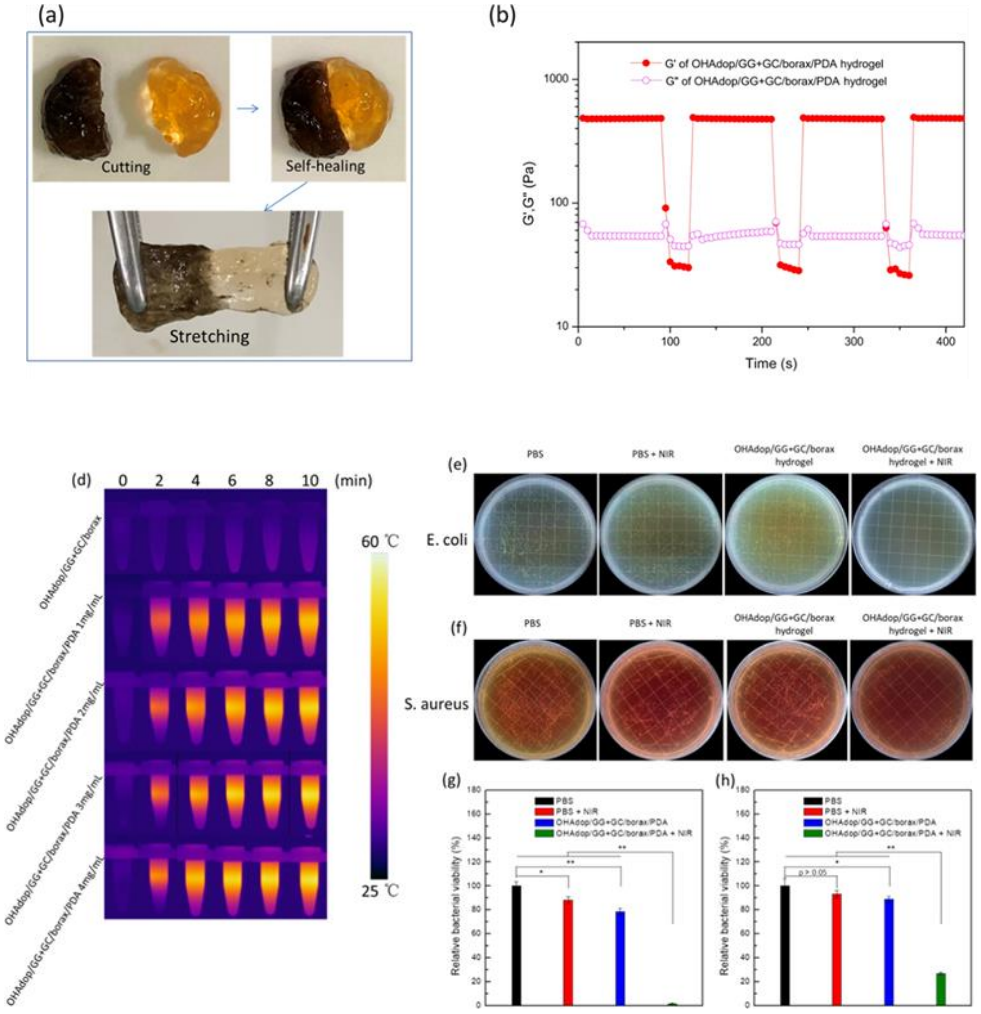

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Figure 1. Preparation and application of the hydrogels. (a) Synthesis of OHAdop. (b) Structure of guar gum (GG). (c) Glycol chitosan (GC) structure. (d) Schematic diagram of the structures and interactions of the dynamically crosslinked hydrogel networks. (e) preparation of the hydrogels. (f) Application of the hydrogels in bacteria-infected wound healing.

0, 3, 7, and 14, and the corresponding wound contractions were calculated.

2.14. Histological Analysis. The wound tissue was collected and stained with H&E and Masson trichrome following our previous work.[60] To assess the inflammatory response and vascular remodeling in the wound area, immunohistochemistry (IHC) stainings for IL-1β and TNF-α and double immunofluorescence (IF) staining for CD31 and α-SMA were performed.

2.15. Statistical Analysis. Group data were reported as the mean standard deviation (SD). Student's test was adopted to calculate the statistical differences (significant for $^{*}p < 0.05$ and very significant for $^{**}p < 0.01$).

3. RESULTS AND DISCUSSION

3.1. Synthesis and Hydrogel Fabrication. Polysaccharides (HA, GG, and GC) were chosen in this work not only for their biocompatibility[36] but also for their ease of modification with functional groups. It was speculated that the reversible crosslinks can contribute to reversible properties of the hydrogel application. Therefore, we designed and prepared polysaccharide-based adhesive hydrogels, which were composed of multiple dynamic bond crosslinked networks of catechol-modified oxidized hyaluronic acid (OHAdop), guar gum (GG), glycol chitosan (GC), borax, and PDA NPs (Figure 1a–d). The formation of a dynamic imine bond between OHAdop and GC, dynamic borate/didiol interactions between GG and borax, and the formation of dynamic hydrogen bonding between the catechol groups in OHAdop or the hydroxide groups in guar gum could result in reversible covalent crosslinking.

OHAdop was synthesized through dopamine-modified OHA to introduce catechol groups. Aldehyde groups could be successfully introduced into the HA backbone via $NaIO_4$ oxidation, as was reported in our previous literature.[63] To improve the adhesive properties, catechol groups were added to the OHA backbone through an EDCI/NHS condensation reaction (see Figure 1a) with dopamine hydrochloride. As seen in Video S1 and Video S2, the OHAdop3% + GC3% hydrogel could adhere to fingers with stretching, while the OHA3% + GC3% hydrogel could not adhere to fingers, which proved improved adhesive properties with the modification of OHA with the catechol group. UV–vis absorption spectroscopy and ^{1}H NMR were carried out to confirm the chemical structure of OHAdop. Similar to the solution of dopamine hydrochloride, OHAdop exhibited strong absorption at λ_{max} = 280 nm, which

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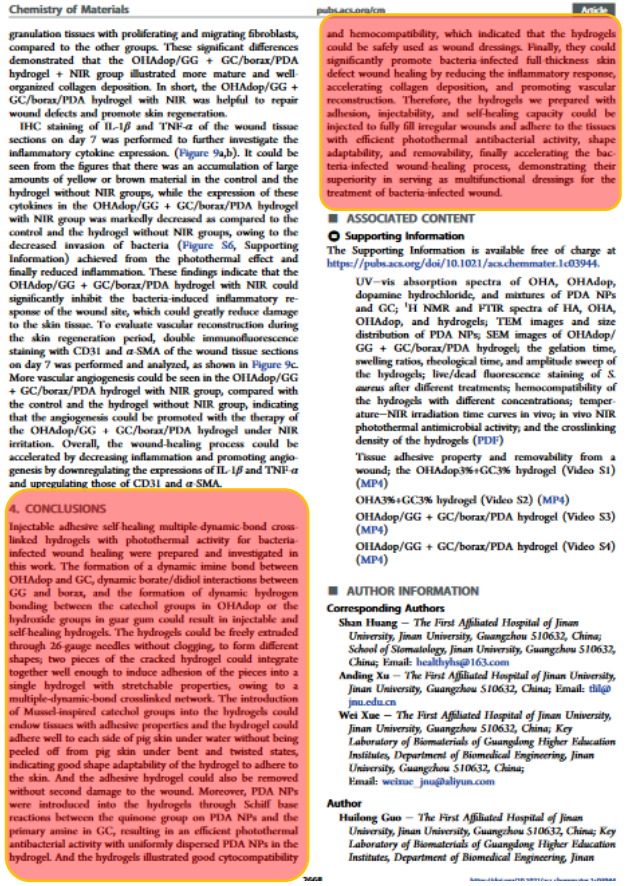

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granulation tissues with proliferating and migrating fibroblasts, compared to the other groups. These significant differences demonstrated that the OHAdop/GG + GC/borax/PDA hydrogel + NIR group illustrated more mature and well-organized collagen deposition. In short, the OHAdop/GG + GC/borax/PDA hydrogel with NIR was helpful to repair wound defects and promote skin regeneration.

IHC staining of IL-1β and TNF-α of the wound tissue sections on day 7 was performed to further investigate the inflammatory cytokine expression. (Figure 9a,b). It could be seen from the figures that there was an accumulation of large amounts of yellow or brown material in the control and the hydrogel without NIR groups, while the expression of these cytokines in the OHAdop/GG + GC/borax/PDA hydrogel with NIR group was markedly decreased as compared to the control and the hydrogel without NIR groups, owing to the decreased invasion of bacteria (Figure S6, Supporting Information) achieved from the photothermal effect and finally reduced inflammation. These findings indicate that the OHAdop/GG + GC/borax/PDA hydrogel with NIR could significantly inhibit the bacteria-induced inflammatory response of the wound site, which could greatly reduce damage to the skin tissue. To evaluate vascular reconstruction during the skin regeneration period, double immunofluorescence staining with CD31 and α-SMA of the wound tissue sections on day 7 was performed and analyzed, as shown in Figure 9c. More vascular angiogenesis could be seen in the OHAdop/GG + GC/borax/PDA hydrogel with NIR group, compared with the control and the hydrogel without NIR group, indicating that the angiogenesis could be promoted with the therapy of the OHAdop/GG + GC/borax/PDA hydrogel under NIR irritation. Overall, the wound-healing process could be accelerated by decreasing inflammation and promoting angiogenesis by downregulating the expressions of IL-1β and TNF-α and upregulating those of CD31 and α-SMA.

4. CONCLUSIONS

Injectable adhesive self-healing multiple-dynamic-bond cross-linked hydrogels with photothermal activity for bacteria-infected wound healing were prepared and investigated in this work. The formation of a dynamic imine bond between OHAdop and GC, dynamic borate/didiol interactions between GG and borax, and the formation of dynamic hydrogen bonding between the catechol groups in OHAdop or the hydroxide groups in guar gum could result in injectable and self-healing hydrogels. The hydrogels could be freely extruded through 26-gauge needles without clogging, to form different shapes; two pieces of the cracked hydrogel could integrate together well enough to induce adhesion of the pieces into a single hydrogel with stretchable properties, owing to a multiple-dynamic-bond crosslinked network. The introduction of Mussel-inspired catechol groups into the hydrogels could endow tissues with adhesive properties and the hydrogel could adhere well to each side of pig skin under water without being peeled off from pig skin under bent and twisted states, indicating good shape adaptability of the hydrogel to adhere to the skin. And the adhesive hydrogel could also be removed without second damage to the wound. Moreover, PDA NPs were introduced into the hydrogels through Schiff base reactions between the quinone group on PDA NPs and the primary amine in GC, resulting in an efficient photothermal antibacterial activity with uniformly dispersed PDA NPs in the hydrogel. And the hydrogels illustrated good cytocompatibility and hemocompatibility, which indicated that the hydrogels could be safely used as wound dressings. Finally, they could significantly promote bacteria-infected full-thickness skin defect wound healing by reducing the inflammatory response, accelerating collagen deposition, and promoting vascular reconstruction. Therefore, the hydrogels we prepared with adhesion, injectability, and self-healing capacity could be injected to fully fill irregular wounds and adhere to the tissues with efficient photothermal antibacterial activity, shape adaptability, and removability, finally accelerating the bacteria-infected wound-healing process, demonstrating their superiority in serving as multifunctional dressings for the treatment of bacteria-infected wound.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemmater.1c03944.

UV−vis absorption spectra of OHA, OHAdop, dopamine hydrochloride, and mixtures of PDA NPs and GC; ^{1}H NMR and FTIR spectra of HA, OHA, OHAdop, and hydrogels; TEM images and size distribution of PDA NPs; SEM images of OHAdop/GG + GC/borax/PDA hydrogel; the gelation time, swelling ratios, rheological time, and amplitude sweep of the hydrogels; live/dead fluorescence staining of *S. aureus* after different treatments; hemocompatibility of the hydrogels with different concentrations; temperature−NIR irradiation time curves in vivo; in vivo NIR photothermal antimicrobial activity; and the crosslinking density of the hydrogels (PDF)

Tissue adhesive property and removability from a wound; the OHAdop3%+GC3% hydrogel (Video S1) (MP4)

OHA3%+GC3% hydrogel (Video S2) (MP4)

OHAdop/GG + GC/borax/PDA hydrogel (Video S3) (MP4)

OHAdop/GG + GC/borax/PDA hydrogel (Video S4) (MP4)

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- UV−vis absorption spectra of OHA, OHAdop, dopamine hydrochloride, and mixtures of PDA NPs and GC; ^{1}H NMR and FTIR spectra of HA, OHA, OHAdop, and hydrogels; TEM images and size distribution of PDA NPs; SEM images of OHAdop/GG + GC/borax/PDA hydrogel; the gelation time, swelling ratios, rheological time, and amplitude sweep of the hydrogels; live/dead fluorescence staining of *S. aureus* after different treatments; hemocompatibility of the hydrogels with different concentrations; temperature−NIR irradiation time curves in vivo; in vivo NIR photothermal antimicrobial activity; and the crosslinking density of the hydrogels (PDF)
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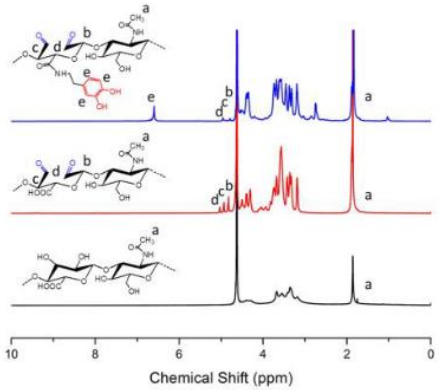
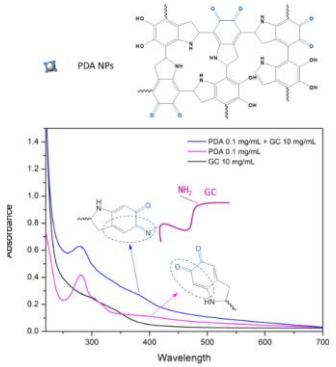
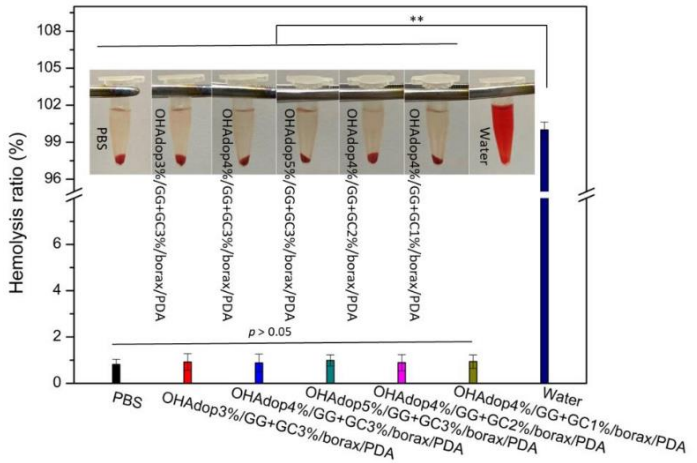
- OHAdop/GG + GC/borax/PDA hydrogel (Video S3) (MP4)
- OHAdop/GG + GC/borax/PDA hydrogel (Video S4) (MP4)







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■ REFERENCES

(1) Zhang, H.; Sun, X.; Wang, J.; Zhang, Y.; Dong, M.; Bu, T.; Li, L.; Liu, Y.; Wang, L. Multifunctional Injectable Hydrogel Dressings for Effectively Accelerating Wound Healing: Enhancing Biomineralization Strategy. *Adv. Funct. Mater.* **2021**, *31*, No. 2100093.

(2) Liang, Y.; Li, Z.; Huang, Y.; Yu, R.; Guo, B. Dual-Dynamic-Bond Cross-Linked Antibacterial Adhesive Hydrogel Sealants with On-Demand Removability for Post-Wound-Closure and Infected Wound Healing. *ACS Nano* **2021**, *15*, 7078−7093.

(3) Zhao, X.; Liang, Y.; Huang, Y.; He, J.; Han, Y.; Guo, B. Physical Double-Network Hydrogel Adhesives with Rapid Shape Adaptability, Fast Self-Healing, Antioxidant and NIR/pH Stimulus-Responsiveness for Multidrug-Resistant Bacterial Infection and Removable Wound Dressing. *Adv. Funct. Mater.* **2020**, *30*, No. 1910748.

(4) Zhang, B.; He, J.; Shi, M.; Liang, Y.; Guo, B. Injectable Self-healing Supramolecular Hydrogels with Conductivity and Photothermal Antibacterial Activity to Enhance Complete Skin Regeneration. *Chem. Eng. J.* **2020**, *400*, No. 125994.

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References

Affram, K., Udofot, O., Singh, M., Krishnan, S., Reams, R., Rosenberg, J., Agyare, E., 2017. Smart thermosensitive liposomes for effective solid tumor therapy and in vivo imaging. PLoS One 12 (9), e0185116.

Aksu, B., Paradkar, A., de Matas, M., Özer, Ö., Güneri, T., York, P., 2012. Quality by design approach: application of artificial intelligence techniques of tablets manufactured by direct compression. AAPS PharmSciTech 13 (4), 1138–1146.

Al-Saidan, S., 2004. Transdermal self-permeation enhancement of ibuprofen. J. Control. Release 100 (2), 199–209.

Altuna, A., Gabriel, G., de la Prida, L.M., Tijero, M., Guimerá, A., Berganzo, J., Salido, R., Villa, R., Fernández, L.J., 2010. SU-8-based microneedles for in vitro neural applications. J. Micromech. Microeng. 20 (6), 064014.

Bagde, A., Patel, K., Kutlehria, S., Chowdhury, N., Singh, M., 2019a. Formulation of topical ibuprofen solid lipid nanoparticle (SLN) gel using hot melt extrusion technique (HME) and determining its anti-inflammatory strength. Drug Deliv. Transl. Res. 9 (4), 816–827.

Bagde, A., Patel, K., Mondal, A., Kutlehria, S., Chowdhury, N., Gebeyehu, A., Patel, N., Kumar, N., Singh, M., 2019b. Combination of UVB absorbing titanium dioxide and quercetin nanogel for skin cancer chemoprevention. AAPS PharmSciTech 20 (6), 1–12.

- Name, Initial.,
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References

[1] J. Fischer, M. Wegener, Three-dimensional optical laser lithography beyond the diffraction limit, Laser Photonics Rev. 7 (2013) 22–44, doi:10.1002/lpor.201100046.

[2] K. Sugioka, Y. Cheng, Femtosecond laser three-dimensional micro-and nanofabrication, Appl. Phys. Rev. 1 (2014) 041303, doi:10.1063/1.4904320.

[3] K. Sugioka, Y. Cheng, Ultrafast lasers – reliable tools for advanced materials processing, Light Sci Appl 3 (2014) e149, doi:10.1038/lsa.2014.30.

[4] K. Sugioka, Hybrid femtosecond laser three-dimensional micro-and nanoprocessing: a review, Int. J. Extrem. Manuf. 1 (2019) 012003, doi:10.1088/2631-7990/ab0eda.

[5] X. Wang, H. Yu, P. Li, Y. Zhang, Femtosecond laser-based processing methods and their applications in optical device manufacturing: a review, Optics & Laser Technology 135 (2021) 106687, doi:10.1016/j.optlastec.2020.106687.

[6] L. Yang, F. Mayer, U.H.F. Bunz, E. Blasco, M. Wegener, Multi-material multiphoton 3D laser micro- and nanoprinting, Light: Adv. Manuf. 2 (2021) 17, doi:10.37188/lam.2021.017.

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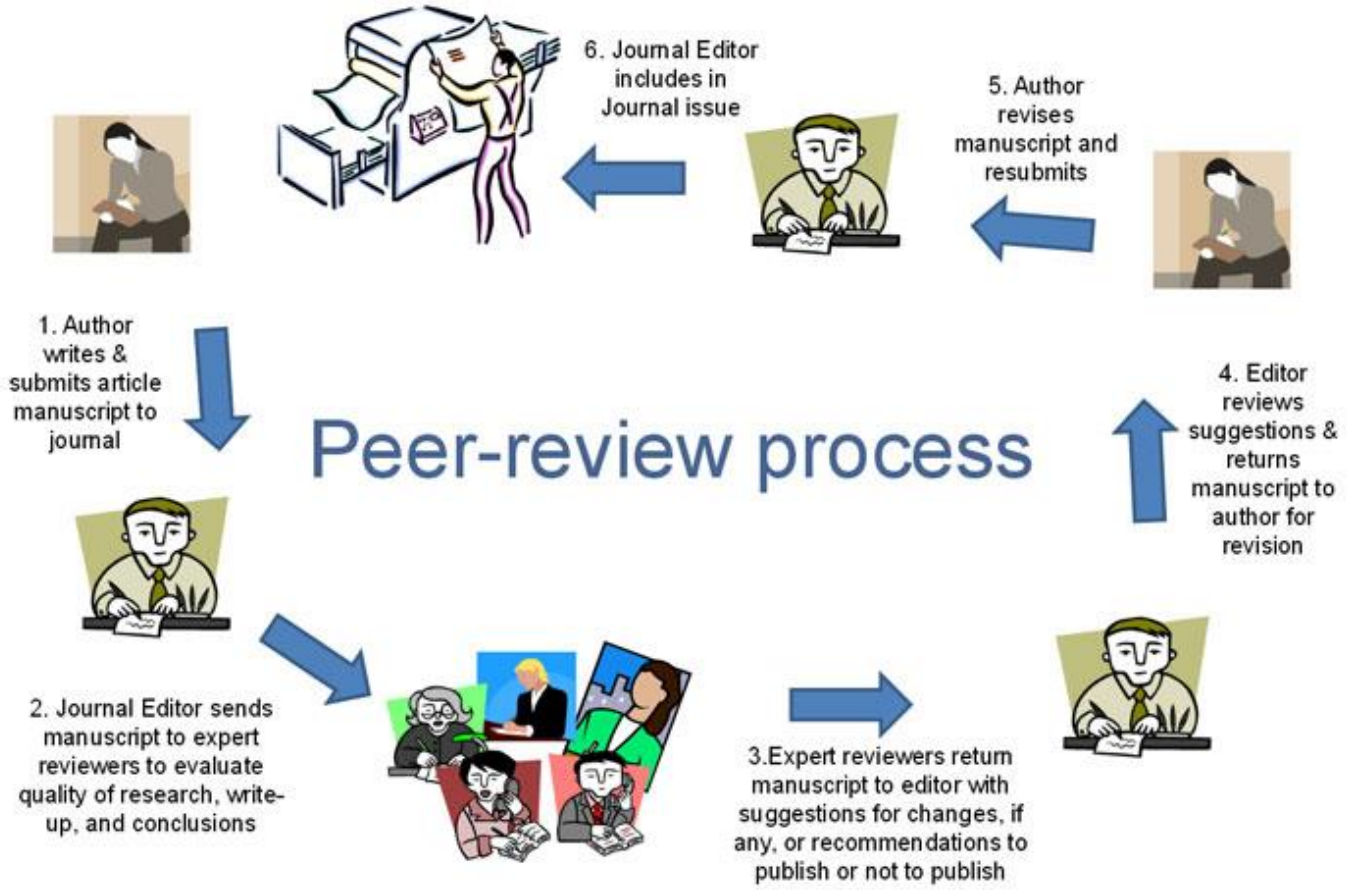

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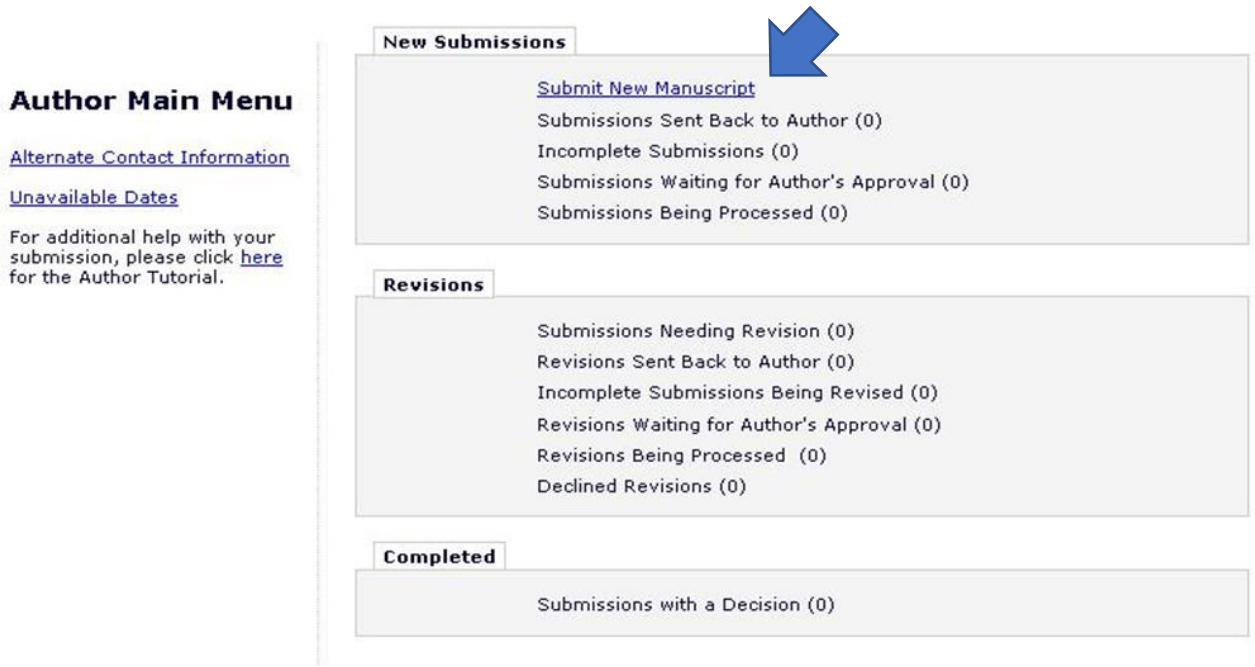

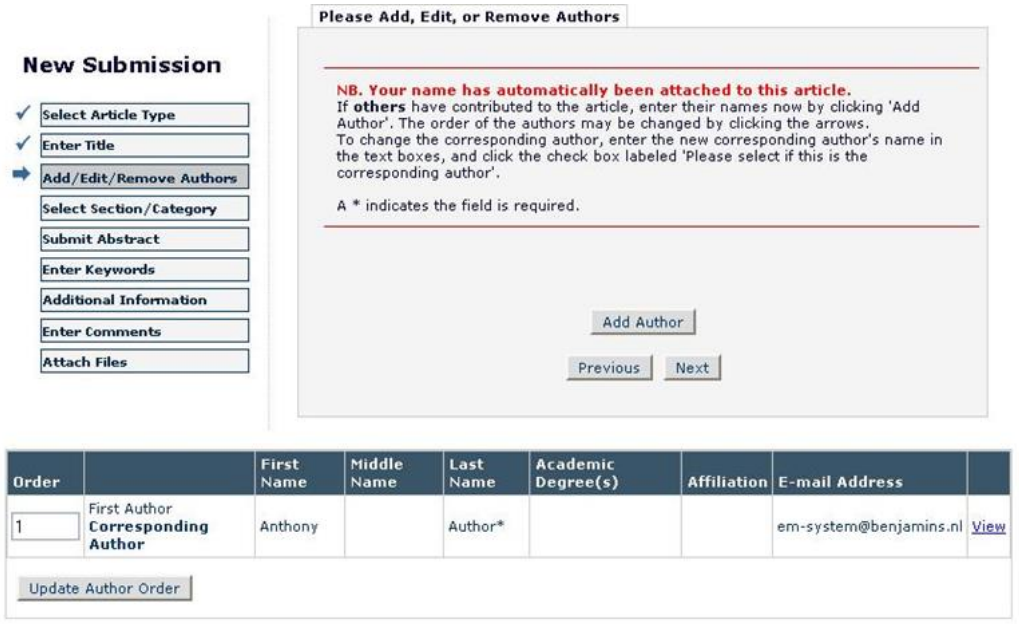

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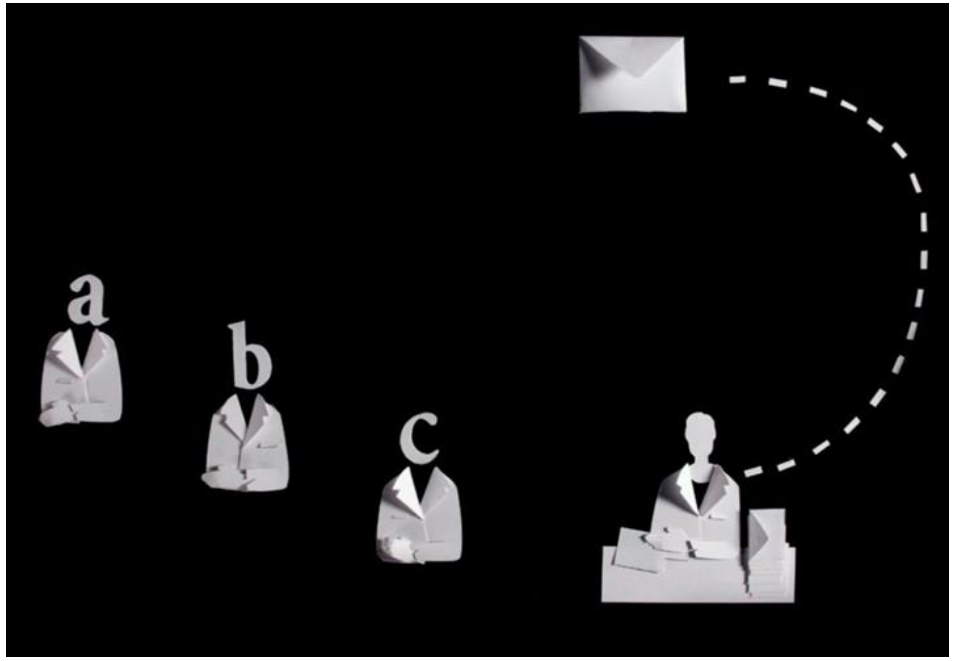

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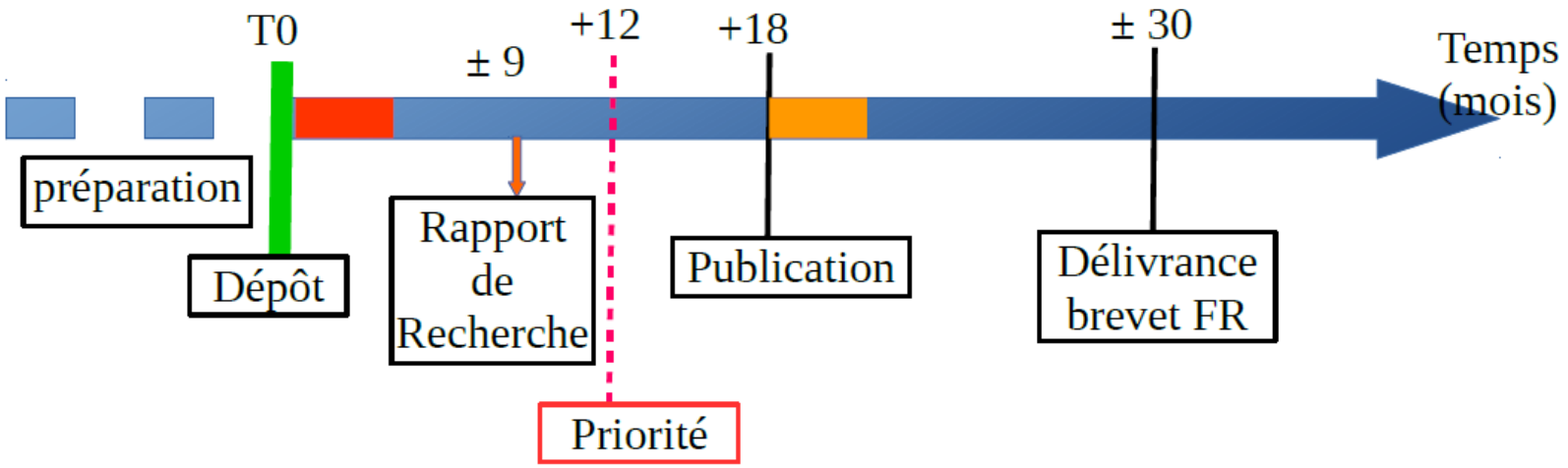

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  - *technicians, service providers, etc… (work under the direction of another person to validate the invention is not alone sufficient to be considered an inventor)*

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(87) International publication number:
WO 2013/127949 (06.09.2013 Gazette 2013/36)

(54) **FUNCTIONAL PLA-PEG COPOLYMERS, THE NANOPARTICLES THEREOF, THEIR PREPARATION AND USE FOR TARGETED DRUG DELIVERY AND IMAGING**

FUNKTIONALE PLA-PEG-COPOLYMERE, NANOPARTIKEL, HERSTELLUNG UND VERWENDUNG ZUR GEZIELTEN ARZNEIMITTELABGABE UND ABBILDUNG

COPOLYMÈRES PLA-PEG FONCTIONNELS, NANOPARTICULES CORRESPONDANTS, LEUR PRÉPARATION ET LEUR UTILISATION POUR L'ADMINISTRATION CIBLÉE DE MÉDICAMENTS ET L'IMAGERIE

EP2820002B1

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Description

[0001] The present invention concerns the field of targeted drug delivery and imaging and in particular the delivery by means of non-covalent encapsulation or conjugation of a drug into a poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) nanoparticle.

[0002] Synthesis of PLA-PEG nanoparticles and their applications in drug delivery has been largely described in the literature. In PLA-PEG composition, PLA (poly(lactic acid)) is hydrophobic and PEG is hydrophilic. PLA-PEG assembles into nanoparticles in aqueous medium, with PLA forming the core and PEG forming the corona. Upon intravenous injection, the PEG corona in the PLA-PEG nanoparticles has been shown to protect the nanoparticle from phagocytosis ("stealth effect") and thus minimize rapid systemic clearance of nanoparticles, and thereby increase their systemic half-life (US patent 5,683,723 describing nanoparticles based on polyoxyethylene and polylactic acid block copolymer). Moreover, such nanoparticles accumulate in tumor by the previously described "Enhanced Permeability and Retention" (EPR) effect. In the field of cancer in particular, tumor specific treatments are desired due to the strong side effects of chemotherapies, and in this context, polymeric nanoparticles have been considered as promising drug delivery systems. When incorporated in the PLA-PEG nanoparticles, the drugs experience prolonged systemic circulation and potentially higher concentration in the tumor due to the EPR effect. In order to deliver the nanoparticle with increased specificity to the tumor, tissue targeting/accumulation approach using homing device could be employed (Pulkkinen et al. Eur J Pharm Biopharm 70 (2008) 66-74, Zhan et al. J Control Rel 143 (2010) 136-142, Farokhzad et al. Cancer Res 64 (2004) 7668-7672, Gao et al. Biomaterials 27 (2006) 3482-3490).

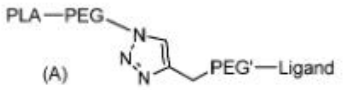
[0003] The use of PLA-PEG nanoparticles further functionalized with a targeting ligand has thus been investigated by the inventors.

[0004] The use of click chemistry (Huisgen coupling) has been described in the literature for the synthesis of different polymeric (Lv et al. J Colloid Interface Sci. 356 (2011) 16-23, Jubeli et al. J Polym Sci Part A: Polym Chem. 48 (2010) 3178-3187, Lecomte et al. Macromol Rapid Commun. 29 (2008) 982-997) or metallic nanoparticle (Hanson et al. US2010/0260676 A1, 2010).

[0005] Click chemistry is of interest because this approach results in high yield, reaction conditions are easy to handle and scalable because the reaction is insensitive to oxygen and water. The background of this reaction is well-known,

Claims

1. A compound of formula (A)



(A)

where:

PLA represents a polylactic acid rest of formula:

FIG.1

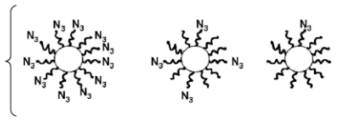


FIG.2

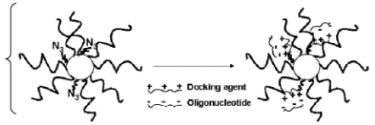
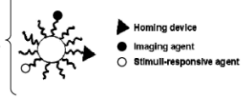


FIG.3



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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5683723 A **[0002] [0062]**
- US 20100260676 A1, Hanson **[0004]**
- WO 2011046946 A **[0007]**
- US 2010104645 A **[0008]**

Non-patent literature cited in the description

- **PULKKINEN et al.** *Eur J Pharm Biopharm*, 2008, vol. 70, 66-74 **[0002]**
- **ZHAN et al.** *J Control Rel*, 2010, vol. 143, 136-142 **[0002]**
- **FAROKHZAD et al.** *Cancer Res*, 2004, vol. 64, 7668-7672 **[0002]**
- **GAO et al.** *Biomaterials*, 2006, vol. 27, 3482-3490 **[0002]**
- **LV et al.** *J Colloid Interface Sci.*, 2011, vol. 356, 16-23 **[0004]**
- **JUBELI et al.** *J Polym Sci Part A: Polym Chem.*, 2010, vol. 48, 3178-3187 **[0004]**
- **LECOMTE et al.** *Macromol Rapid Commun.*, 2008, vol. 29, 982-997 **[0004]**
- **DESHAYES et al.** *Pharm. Res.*, 2011, vol. 28, 1631-1642 **[0006]**
- **TANG et al.** *Macromolecules*, 2011, vol. 44, 1491-1499 **[0006]**
- **YU et al.** *Macromolecules*, 2011, vol. 44 (12), 4793-4800 **[0006]**
- **LU et al.** *Bioconjugate Chem*, 2009, vol. 20, 87-94 **[0006]**
- **ZHANG et al.** *Mol. Pharmaceutics*, 2012, vol. 9, 2228-2236 **[0007]**
- **XIAO et al.** *International Journal of nanomedicine*, 2010, vol. 5 (1), 1057-1065 **[0007]**
- **ARUTSELVAN et al.** *Chemical Communications*, 2007, vol. 7, 695-697 **[0007]**
- **STEINMETZ et al.** *Journal of the American Chemical Society*, 2009, vol. 131 (47), 17093-17095 **[0007]**
- **ADIBEKIAN et al.** *Nature Chemical Biology*, 2011, vol. 7, 469-479 **[0007]**
- *Chem. Rev.*, 2008, vol. 108, 2952-3015 **[0057] [0059] [0060]**
- **P.G.M. WUTS ; T.W. GREENE.** Greene's Protective Groups in Organic Synthesis. John Wiley & Sons, 2007 **[0083]**
- **J. F. W. MCOMIE.** Protective Groups in Organic Chemistry. Plenum Press, 1973 **[0083]**
- **J. MARCH.** Advances in Organic Chemistry. Wiley Interscience, 310-316 **[0087]**
- **R.C. LAROCK.** Comprehensive Organic Transformations. VCH publishers, 1989 **[0119]**
- **NICOLAS et al.** *Macromol*, 2008 **[0178]**
- **JOHNSON et al.** *Anal. Biochem.*, 1991, vol. 198, 268-277 **[0215]**

Ethical principles

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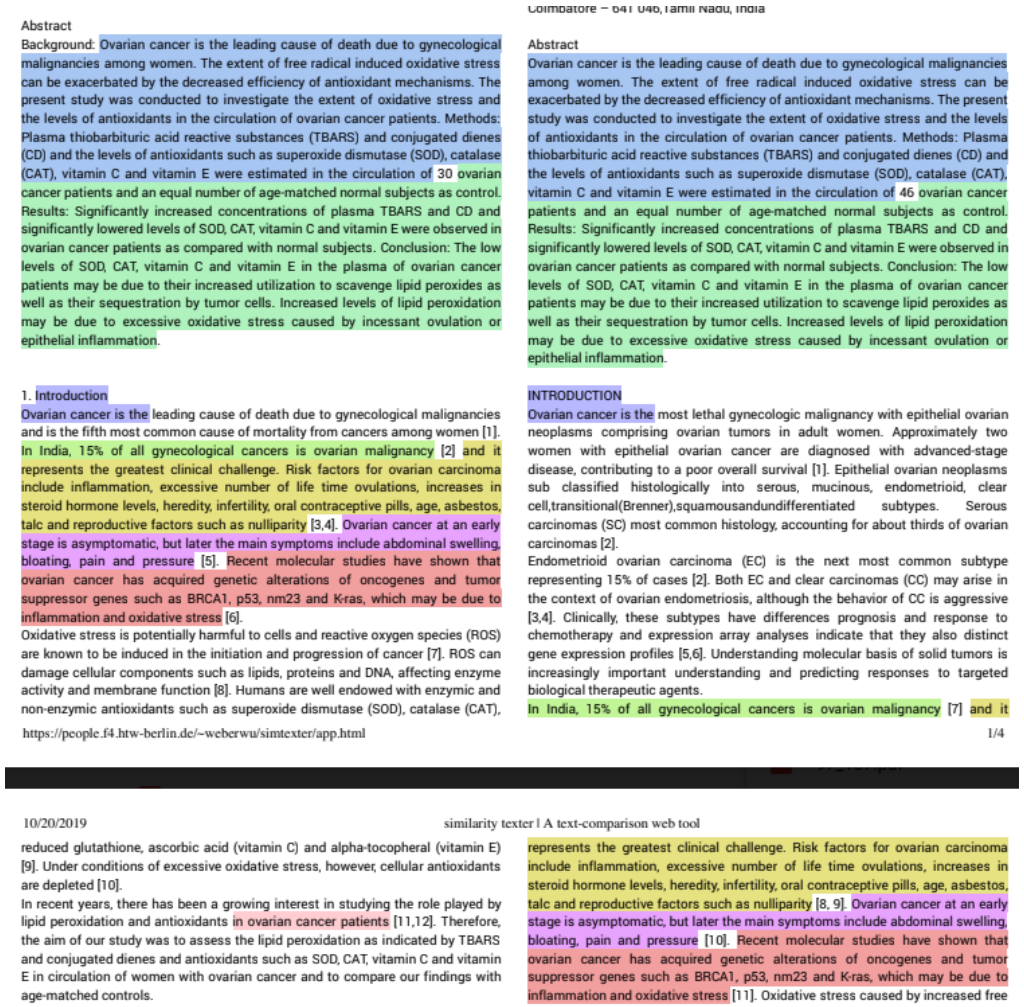

Coimbatore – 641 046, Tamil Nadu, India

Abstract

Background: Ovarian cancer is the leading cause of death due to gynecological malignancies among women. The extent of free radical induced oxidative stress can be exacerbated by the decreased efficiency of antioxidant mechanisms. The present study was conducted to investigate the extent of oxidative stress and the levels of antioxidants in the circulation of ovarian cancer patients. Methods: Plasma thiobarbituric acid reactive substances (TBARS) and conjugated dienes (CD) and the levels of antioxidants such as superoxide dismutase (SOD), catalase (CAT), vitamin C and vitamin E were estimated in the circulation of 30 ovarian cancer patients and an equal number of age-matched normal subjects as control. Results: Significantly increased concentrations of plasma TBARS and CD and significantly lowered levels of SOD, CAT, vitamin C and vitamin E were observed in ovarian cancer patients as compared with normal subjects. Conclusion: The low levels of SOD, CAT, vitamin C and vitamin E in the plasma of ovarian cancer patients may be due to their increased utilization to scavenge lipid peroxides as well as their sequestration by tumor cells. Increased levels of lipid peroxidation may be due to excessive oxidative stress caused by incessant ovulation or epithelial inflammation.

1. Introduction

Ovarian cancer is the leading cause of death due to gynecological malignancies and is the fifth most common cause of mortality from cancers among women [1]. In India, 15% of all gynecological cancers is ovarian malignancy [2] and it represents the greatest clinical challenge. Risk factors for ovarian carcinoma include inflammation, excessive number of life time ovulations, increases in steroid hormone levels, heredity, infertility, oral contraceptive pills, age, asbestos, talc and reproductive factors such as nulliparity [3,4]. Ovarian cancer at an early stage is asymptomatic, but later the main symptoms include abdominal swelling, bloating, pain and pressure [5]. Recent molecular studies have shown that ovarian cancer has acquired genetic alterations of oncogenes and tumor suppressor genes such as BRCA1, p53, nm23 and K-ras, which may be due to inflammation and oxidative stress [6].

Oxidative stress is potentially harmful to cells and reactive oxygen species (ROS) are known to be induced in the initiation and progression of cancer [7]. ROS can damage cellular components such as lipids, proteins and DNA, affecting enzyme activity and membrane function [8]. Humans are well endowed with enzymic and non-enzymic antioxidants such as superoxide dismutase (SOD), catalase (CAT),

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Abstract

Ovarian cancer is the leading cause of death due to gynecological malignancies among women. The extent of free radical induced oxidative stress can be exacerbated by the decreased efficiency of antioxidant mechanisms. The present study was conducted to investigate the extent of oxidative stress and the levels of antioxidants in the circulation of ovarian cancer patients. Methods: Plasma thiobarbituric acid reactive substances (TBARS) and conjugated dienes (CD) and the levels of antioxidants such as superoxide dismutase (SOD), catalase (CAT), vitamin C and vitamin E were estimated in the circulation of 46 ovarian cancer patients and an equal number of age-matched normal subjects as control. Results: Significantly increased concentrations of plasma TBARS and CD and significantly lowered levels of SOD, CAT, vitamin C and vitamin E were observed in ovarian cancer patients as compared with normal subjects. Conclusion: The low levels of SOD, CAT, vitamin C and vitamin E in the plasma of ovarian cancer patients may be due to their increased utilization to scavenge lipid peroxides as well as their sequestration by tumor cells. Increased levels of lipid peroxidation may be due to excessive oxidative stress caused by incessant ovulation or epithelial inflammation.

INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy with epithelial ovarian neoplasms comprising ovarian tumors in adult women. Approximately two women with epithelial ovarian cancer are diagnosed with advanced-stage disease, contributing to a poor overall survival [1]. Epithelial ovarian neoplasms sub classified histologically into serous, mucinous, endometrioid, clear cell,transitional(Brenner),squamousandundifferentiated subtypes. Serous carcinomas (SC) most common histology, accounting for about thirds of ovarian carcinomas [2].

Endometrioid ovarian carcinoma (EC) is the next most common subtype representing 15% of cases [2]. Both EC and clear carcinomas (CC) may arise in the context of ovarian endometriosis, although the behavior of CC is aggressive [3,4]. Clinically, these subtypes have differences prognosis and response to chemotherapy and expression array analyses indicate that they also distinct gene expression profiles [5,6]. Understanding molecular basis of solid tumors is increasingly important understanding and predicting responses to targeted biological therapeutic agents.

In India, 15% of all gynecological cancers is ovarian malignancy [7] and it

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reduced glutathione, ascorbic acid (vitamin C) and alpha-tocopheral (vitamin E) [9]. Under conditions of excessive oxidative stress, however, cellular antioxidants are depleted [10].

In recent years, there has been a growing interest in studying the role played by lipid peroxidation and antioxidants in ovarian cancer patients [11,12]. Therefore, the aim of our study was to assess the lipid peroxidation as indicated by TBARS and conjugated dienes and antioxidants such as SOD, CAT, vitamin C and vitamin E in circulation of women with ovarian cancer and to compare our findings with age-matched controls.

represents the greatest clinical challenge. Risk factors for ovarian carcinoma include inflammation, excessive number of life time ovulations, increases in steroid hormone levels, heredity, infertility, oral contraceptive pills, age, asbestos, talc and reproductive factors such as nulliparity [8, 9]. Ovarian cancer at an early stage is asymptomatic, but later the main symptoms include abdominal swelling, bloating, pain and pressure [10]. Recent molecular studies have shown that ovarian cancer has acquired genetic alterations of oncogenes and tumor suppressor genes such as BRCA1, p53, nm23 and K-ras, which may be due to inflammation and oxidative stress [11]. Oxidative stress caused by increased free

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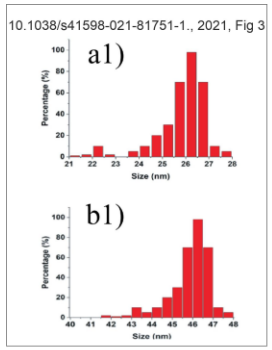

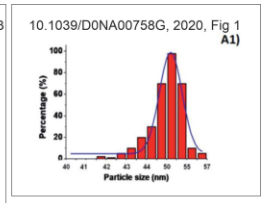

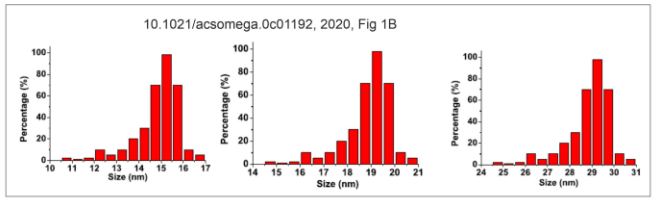

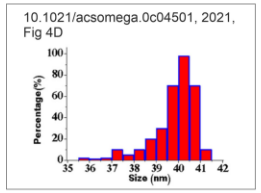

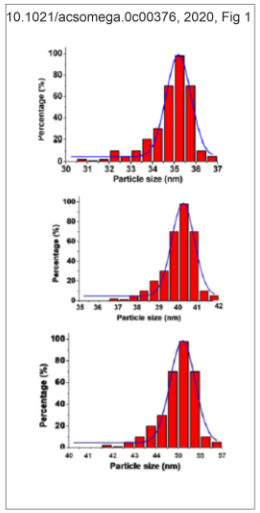

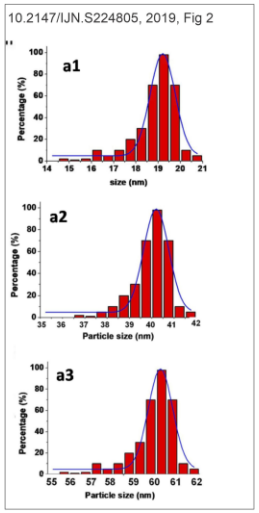

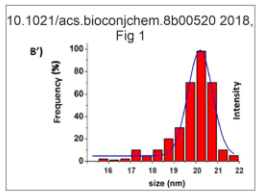

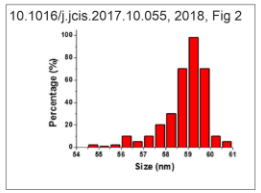

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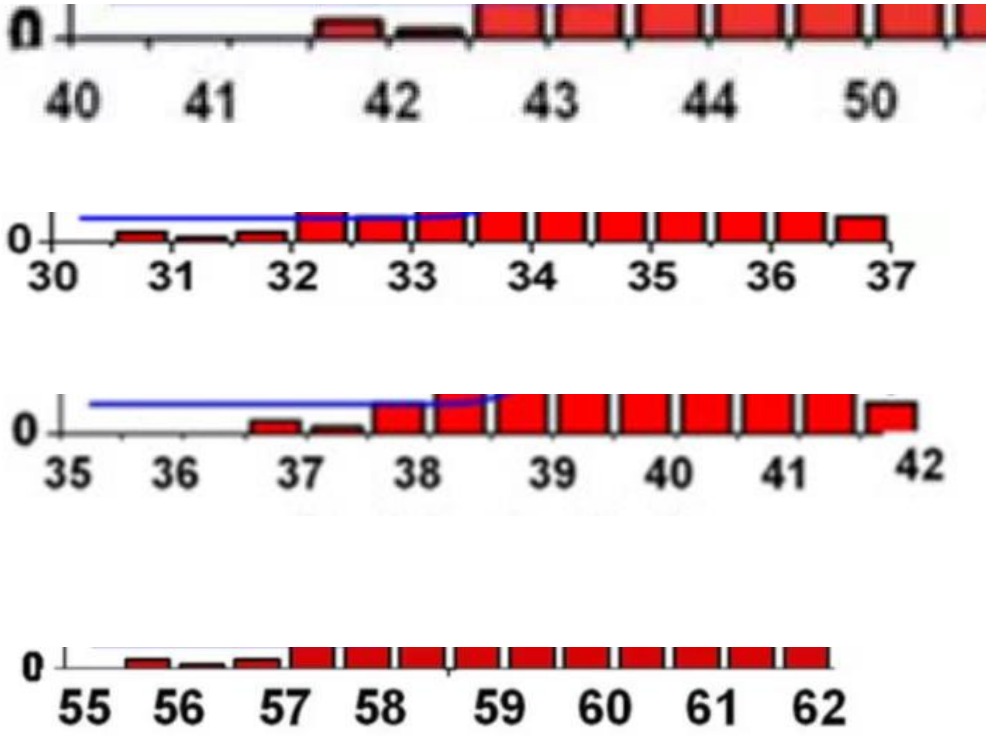

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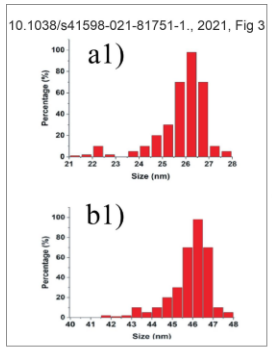

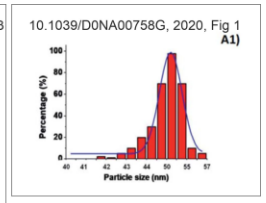

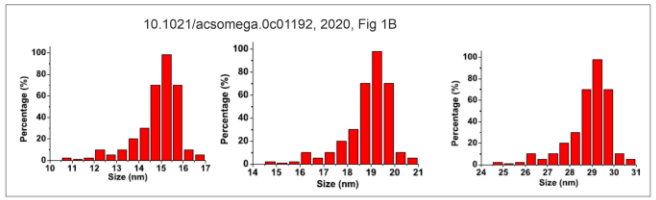

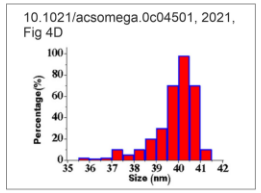

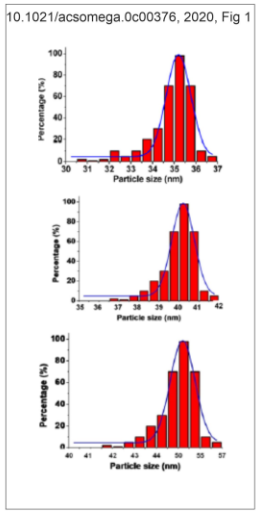

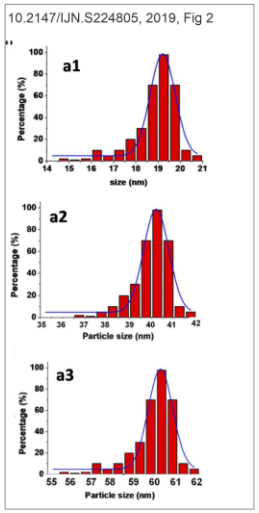

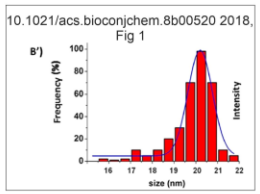

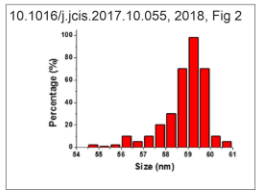

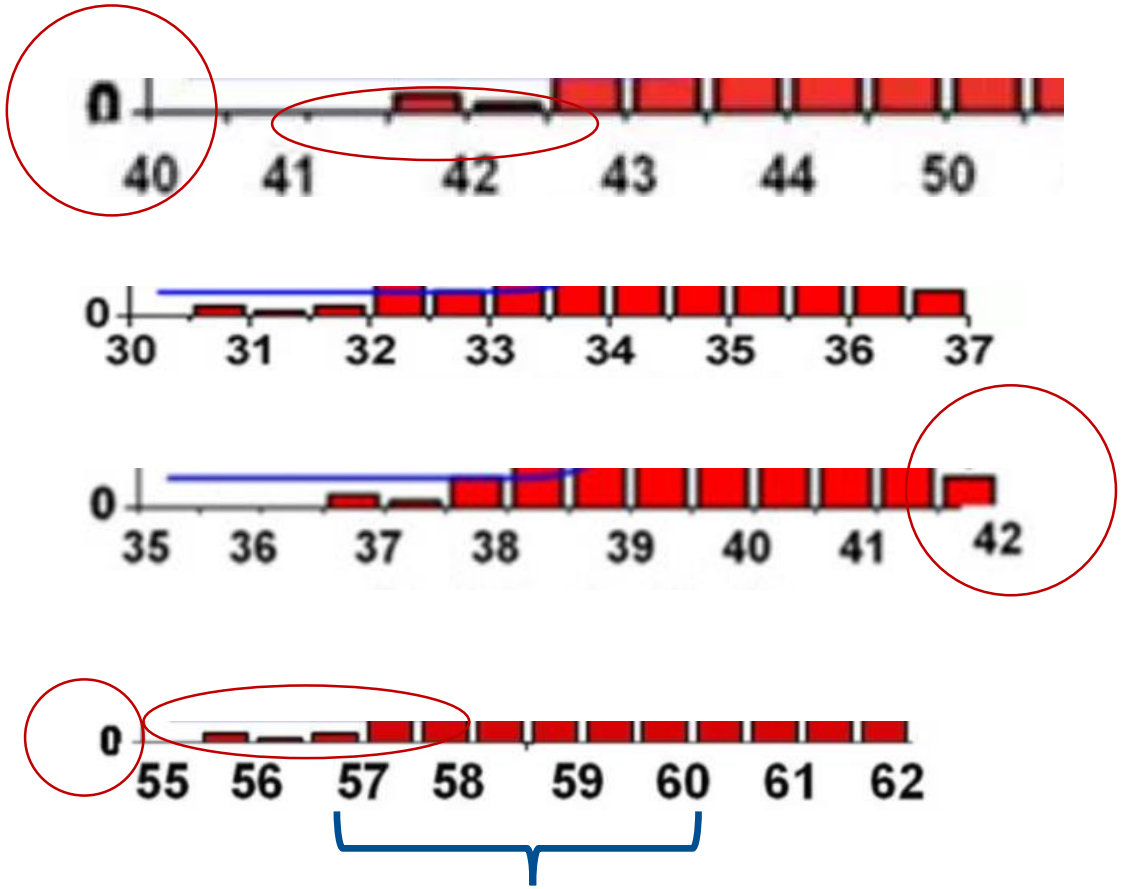

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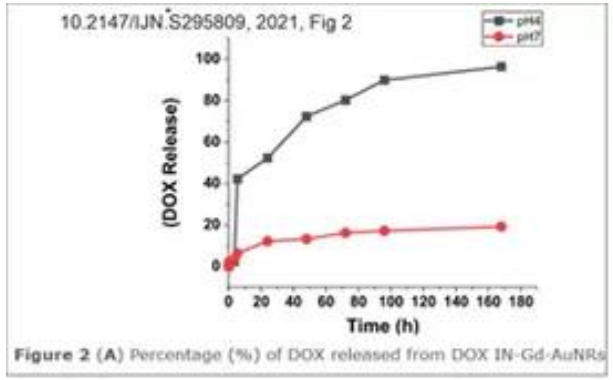

Figure 2 (A) Percentage (%) of DOX released from DOX IN-Gd-AuNRs

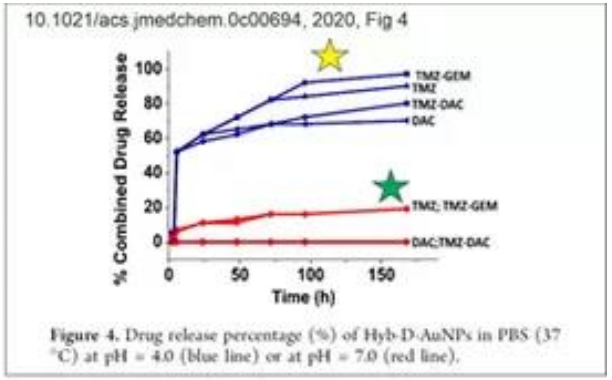

Figure 4. Drug release percentage (%) of Hyb-D-AuNPs in PBS (37 °C) at pH = 4.0 (blue line) or at pH = 7.0 (red line).

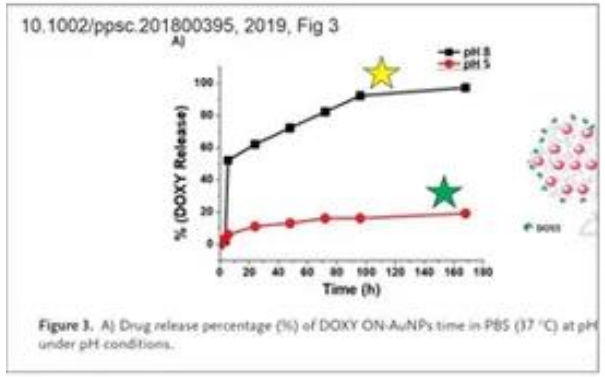

Figure 3. A) Drug release percentage (%) of DOXY ON-AuNPs time in PBS (37 °C) at pH under pH conditions.

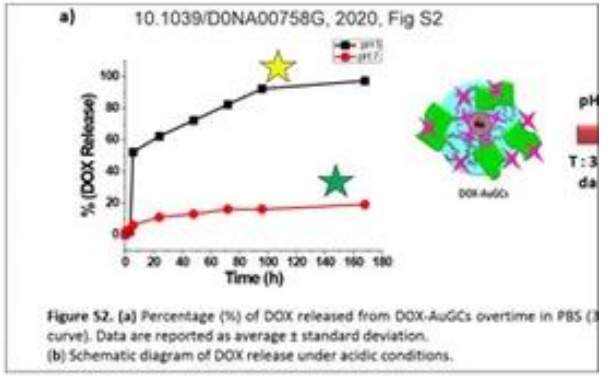

Figure S2. (a) Percentage (%) of DOX released from DOX-AuGCs overtime in PBS (3 curve). Data are reported as average ± standard deviation.
(b) Schematic diagram of DOX release under acidic conditions.

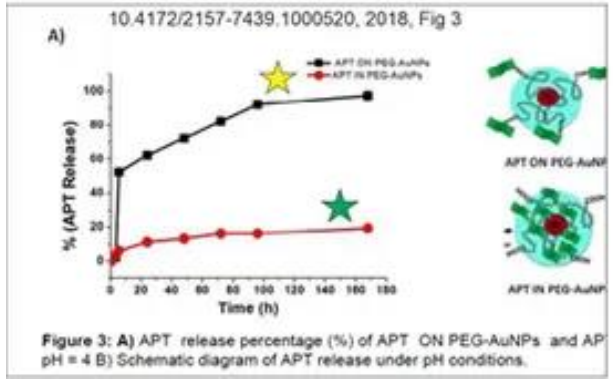

Figure 3: A) APT release percentage (%) of APT ON PEG-AuNPs and AP pH = 4 B) Schematic diagram of APT release under pH conditions.

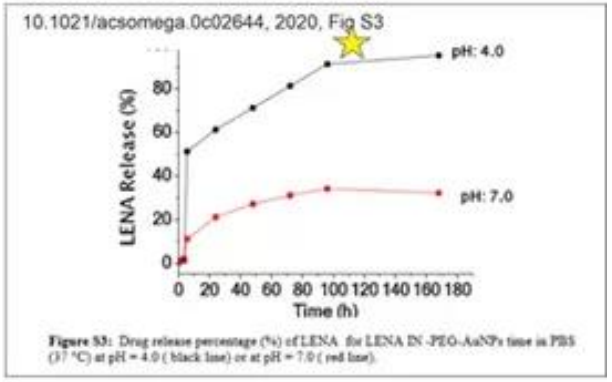

Figure S3: Drug release percentage (%) of LENA for LENA IN -PEG-AuNPs time in PBS (37 °C) at pH = 4.0 (black line) or at pH = 7.0 (red line).

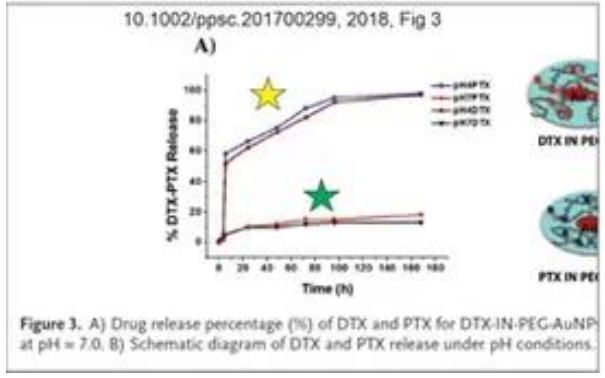

Figure 3. A) Drug release percentage (%) of DTX and PTX for DTX-IN-PEG-AuNP at pH = 7.0. B) Schematic diagram of DTX and PTX release under pH conditions.

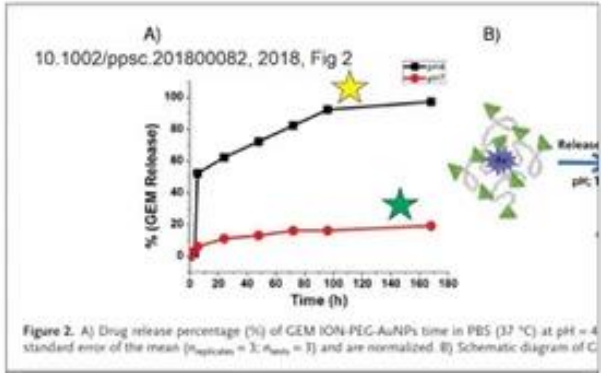

Figure 2. A) Drug release percentage (%) of GEM ION-PEG-AuNPs time in PBS (37 °C) at pH = 4 standard error of the mean ($n_{replicates}$ = 3; n_{tests} = 3) and are normalized. B) Schematic diagram of G

Different drugs and different systems

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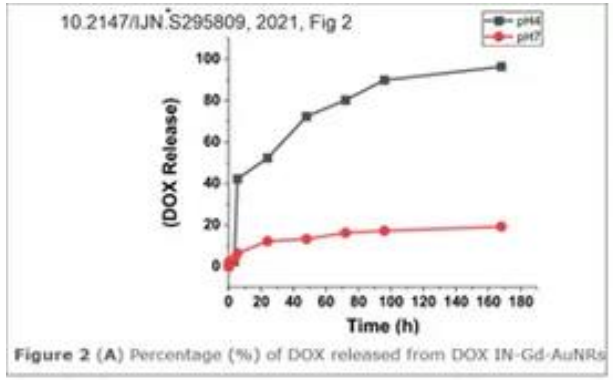

Figure 2 (A) Percentage (%) of DOX released from DOX IN-Gd-AuNRs

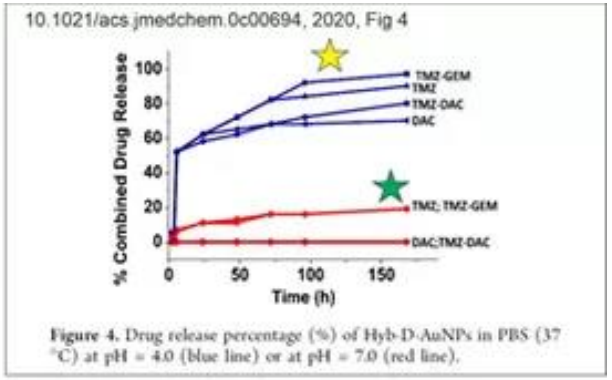

Figure 4. Drug release percentage (%) of Hyb-D-AuNPs in PBS (37 °C) at pH = 4.0 (blue line) or at pH = 7.0 (red line).

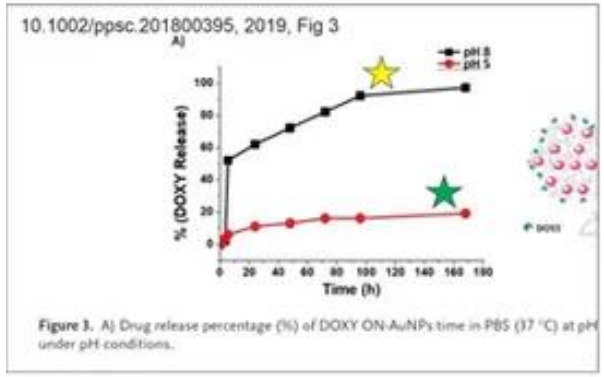

Figure 3. A) Drug release percentage (%) of DOXY ON-AuNPs time in PBS (37 °C) at pH under pH conditions.

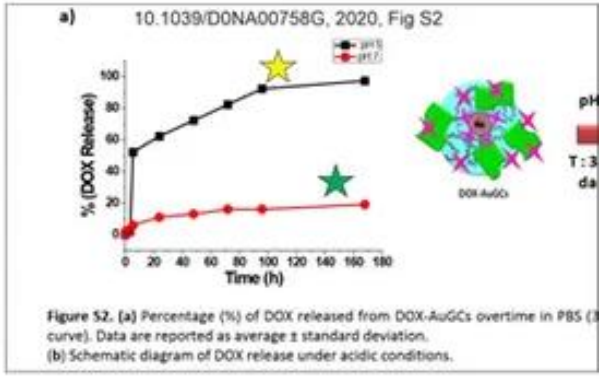

Figure S2. (a) Percentage (%) of DOX released from DOX-AuGCs overtime in PBS (3 curve). Data are reported as average ± standard deviation.
(b) Schematic diagram of DOX release under acidic conditions.

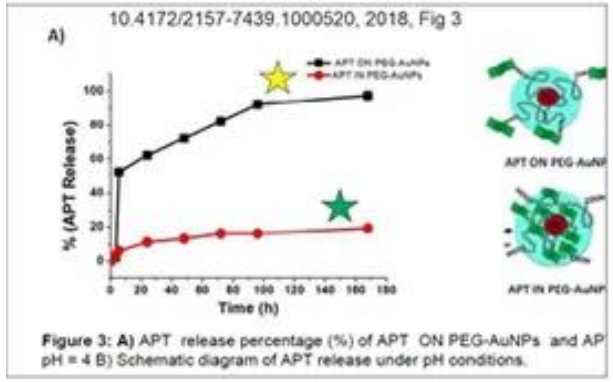

Figure 3: A) APT release percentage (%) of APT ON PEG-AuNPs and AP pH = 4 B) Schematic diagram of APT release under pH conditions.

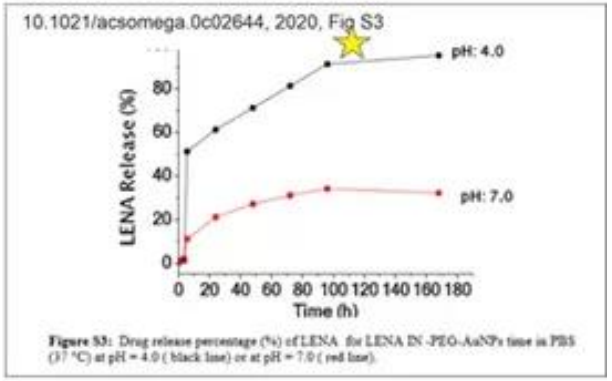

Figure S3: Drug release percentage (%) of LENA for LENA IN -PEG-AuNPs time in PBS (37 °C) at pH = 4.0 (black line) or at pH = 7.0 (red line).

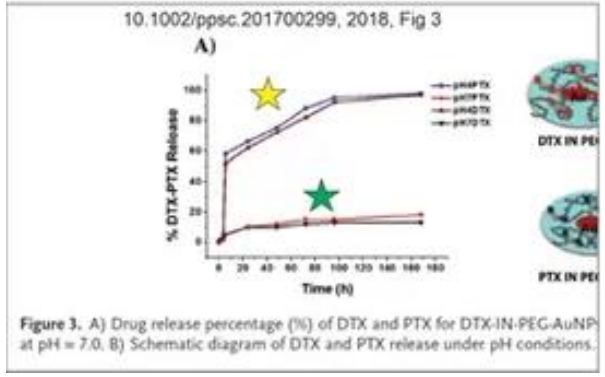

Figure 3. A) Drug release percentage (%) of DTX and PTX for DTX-IN-PEG-AuNP at pH = 7.0. B) Schematic diagram of DTX and PTX release under pH conditions.

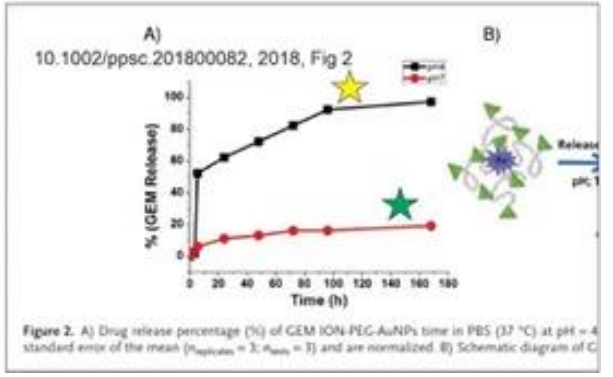

Figure 2. A) Drug release percentage (%) of GEM ION-PEG-AuNPs time in PBS (37 °C) at pH = 4 standard error of the mean ($n_{replicates}$ = 3; n_{tests} = 3) and are normalized. B) Schematic diagram of G

Different drugs and different systems

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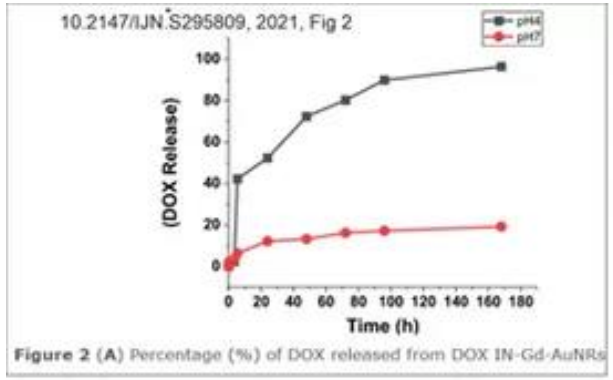
Ethical principles

Research Misconduct: Data Falsification and / or data fabrication



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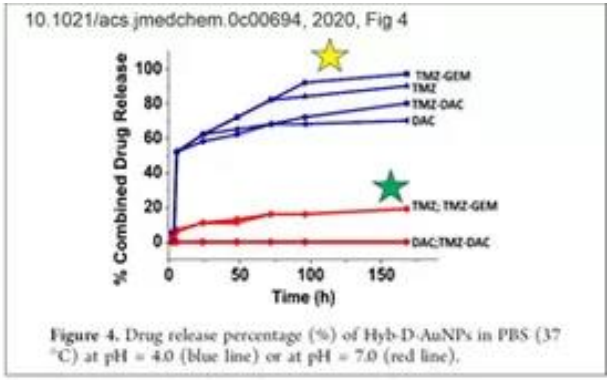

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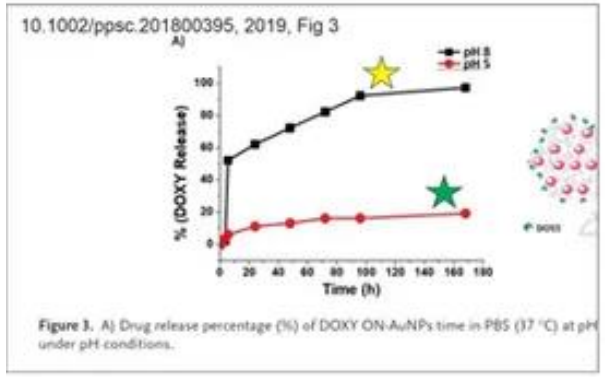
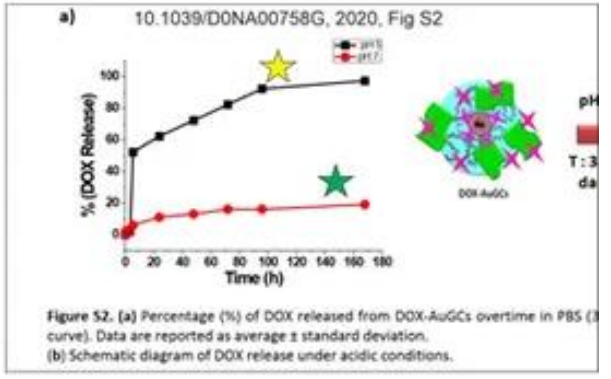


Figure 3. A) Drug release percentage (%) of DOXY ON-AuNPs time in PBS (37 °C) at pH under pH conditions.



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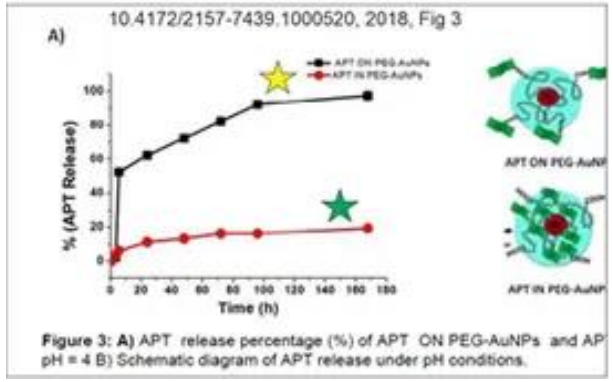

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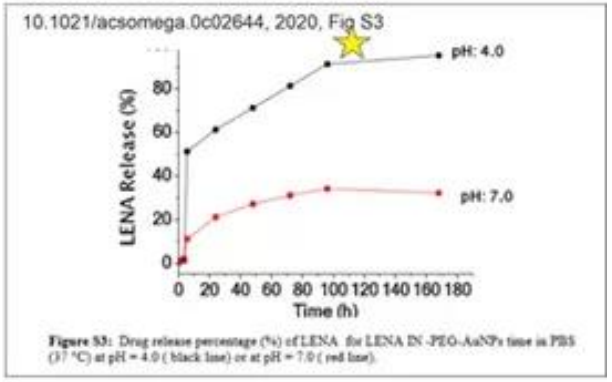
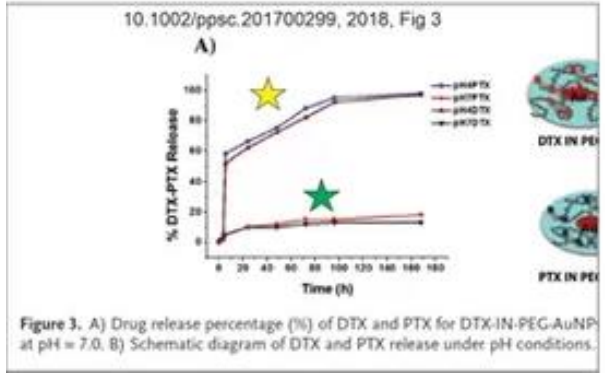


Figure S3: Drug release percentage (%) of LENA for LENA IN -PEG-AuNPs time in PBS (37 °C) at pH = 4.0 (black line) or at pH = 7.0 (red line).



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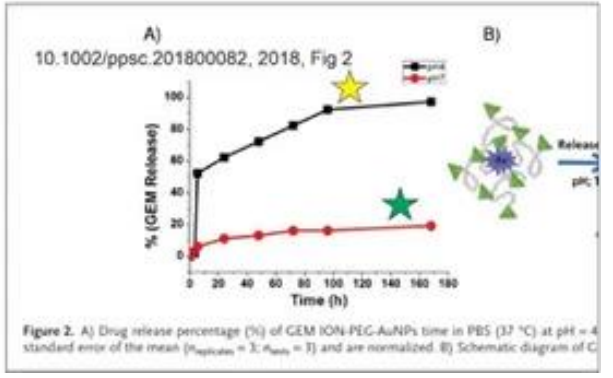

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Different drugs and different systems

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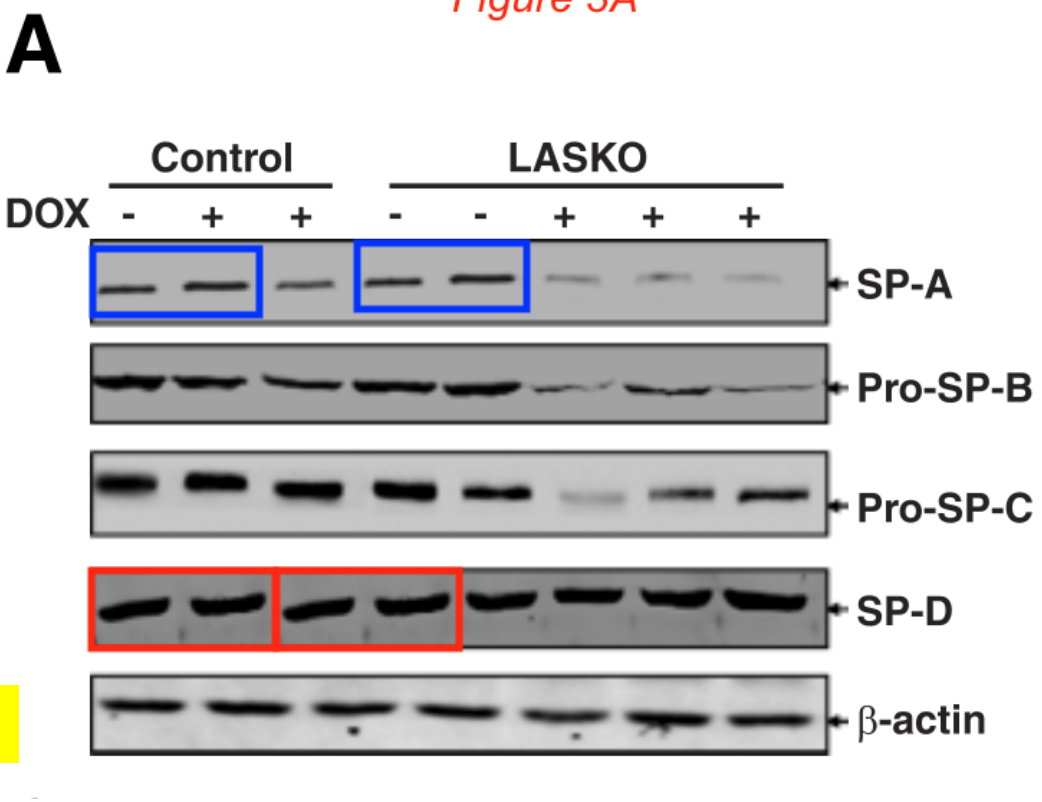
Ethical principles

Research Misconduct: Data Falsification and / or data fabrication

Xue Zhang et al., DOI: 10.1096/fj.11-200139
Figure 3A



Duplication

Only 7 lines…

https://pubpeer.com/publications/FA510E0DEEEEBAA91CA7D2E4F40DA3

Ethical principles

Research Misconduct: Data Falsification and / or data fabrication

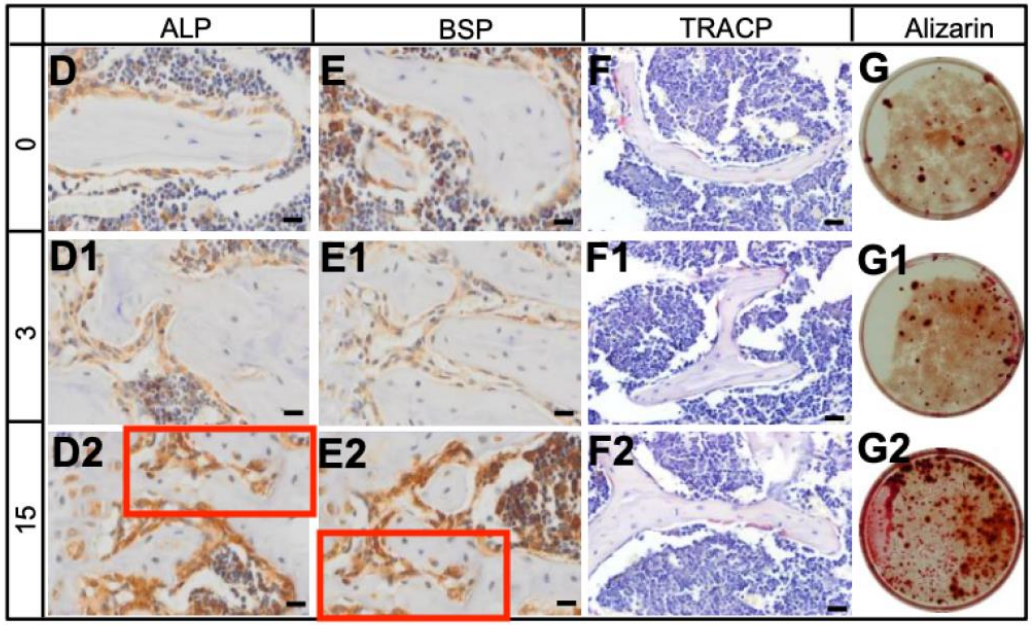


Figure 3, detail - DOI: 10.1016/j.jsbmb.2017.04.004

Figure 2a

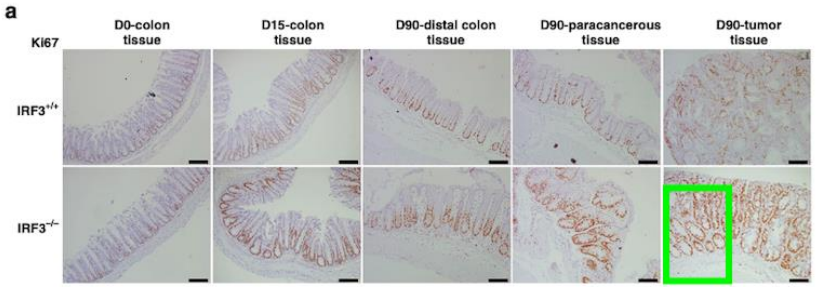
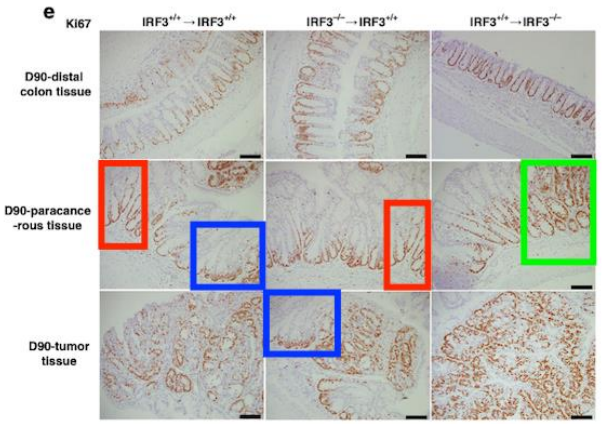


Figure 2e (chimera mice)



Overlap : same sample?

https://pubpeer.com/publications/A3B1102AD22F9F6C174820A2666BB5
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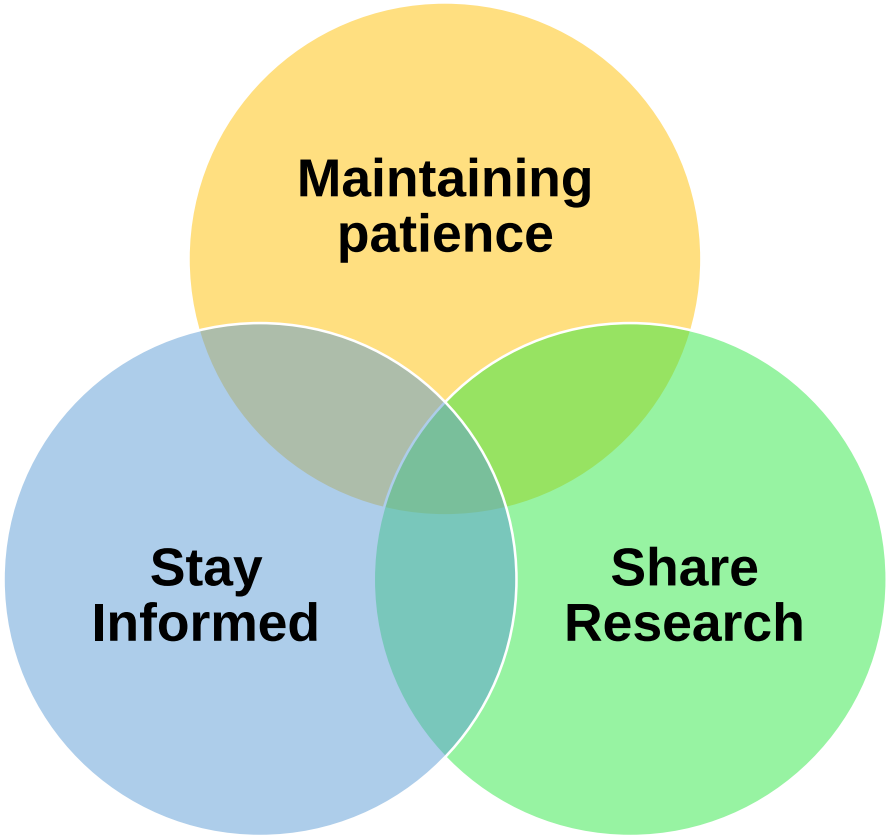
Doing research



Q&A