

Le Fucoïdane, un polysaccharide sulfaté d'algues brunes

Depuis son extraction sur les côtes bretonnes
jusqu'aux essais cliniques

D. Letourneur

CONGRÈS FRANÇAIS
d'HÉMOSTASE

10-12
MAI
2023

PROGRAMME



The journey started here...

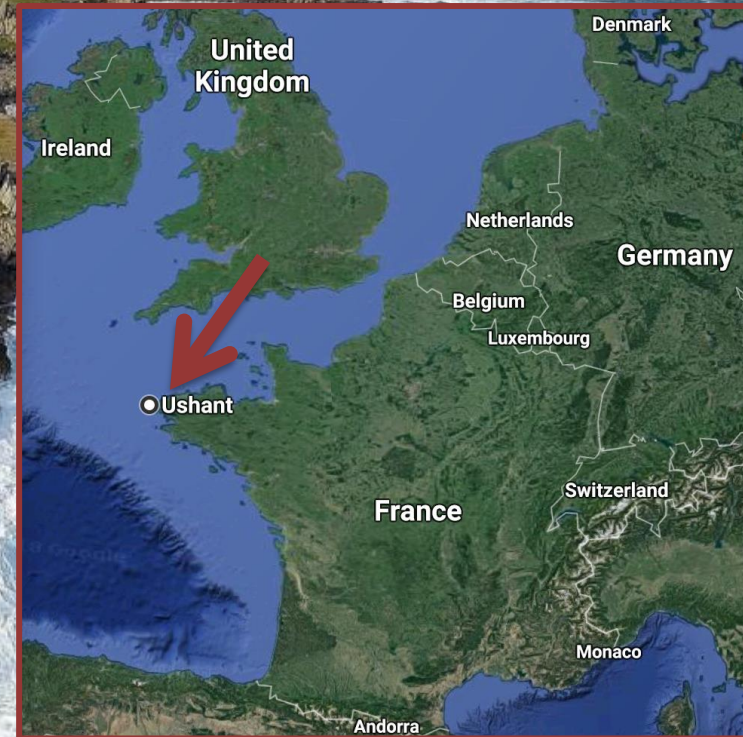
Ushant island (Brittany coast, France)



**Production of Fucoxanthin
from brown seaweeds**

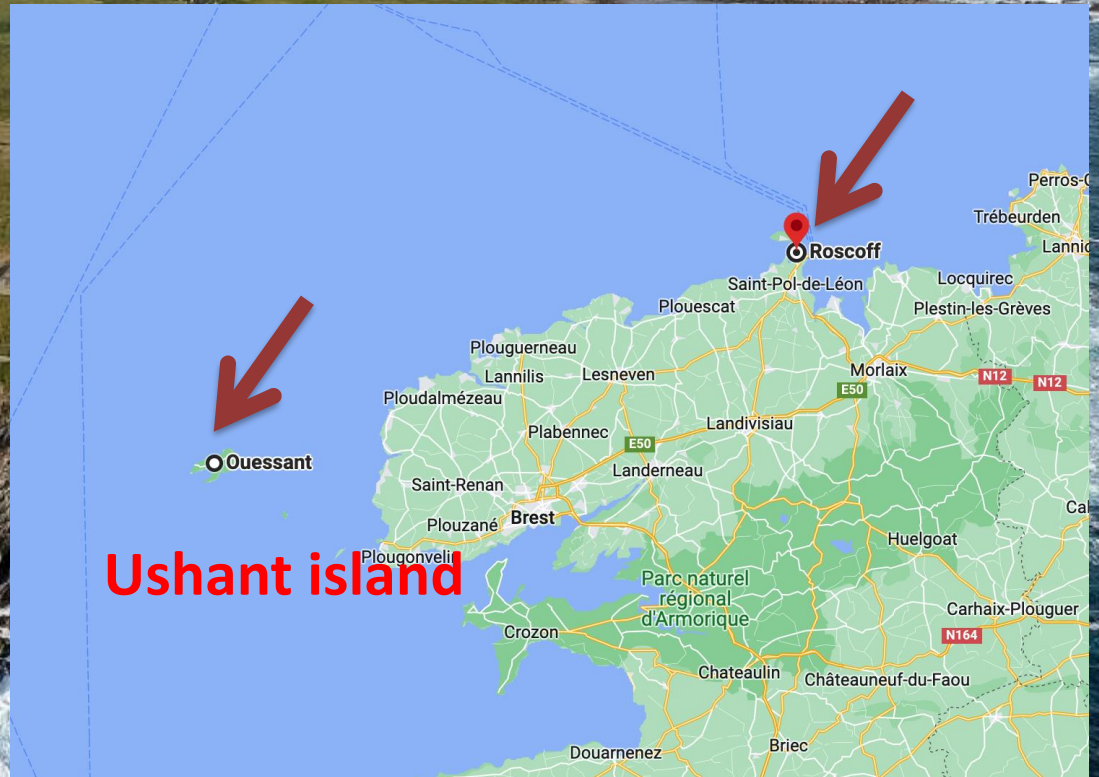
The journey started here...

Ushant island (Brittany coast, France)



**Production of Fucoidan
from brown seaweeds**

The journey started also here (Roscoff)



The journey started also here (Roscoff)



CNRS • SORBONNE UNIVERSITÉ
Station Biologique
de Roscoff

SECTIONS



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de Roscoff

SCIENCES
SORBONNE
UNIVERSITÉ



UMR Adaptation et Diversité en Milieu Marin Unité de recherche UMR7144

PRÉSENTATION DE L'UNITÉ

EQUIPES DE RECHERCHE

RECRUTEMENTS ET STAGES

INTRANET

ACTUALITÉ

MEMBRES

ARCHIVES HAL



The journey started here...



... and became National & International

The journey started with... (1989)



Biomaterials

Volume 10, Issue 6, August 1989, Pages 363-368



New natural polysaccharides with potent antithrombic activity: fucans from brown algae

V. Grauffel *, B. Kloareg **, S. Mabeau **, P. Durand †, J. Jozefonvicz * 

* Laboratoire de Recherches sur les Macromolécules, CNRS UA 502, Université Paris-Nord, Av. J.B. Clément, 93430 Villetaneuse, France

** Centre d'Etudes Océanologiques et de Biologie Marine, CNRS LP 4601, Place G. Tessiers, 29211 Roscoff, France

† Département Utilisation et Valorisation des Produits de la Mer, IFREMER, rue de l'Île d'Yeu, BP 1049, 44037 Nantes cédex, France

A long and not linear journey

Comparative Study > Eur J Cell Biol. 1997 Dec;74(4):376-84.

Fucans, sulfated polysaccharides extracted from brown seaweeds, inhibit vascular smooth muscle cell proliferation. I. Comparison with heparin for antiproliferative activity, binding and internalization

D Logeart ¹, S Prigent-Richard, J Jozefonvicz, D Letourneur

Affiliations + expand

PMID: 9438134

Abstract

Smooth muscle cell (SMC) proliferation is inhibited both in vivo and in vitro by heparin. However, the precise mechanisms of action are still not understood. The analogy between two sulfated polysaccharides, heparin and fucan, has led us to compare in detail their effects on SMC growth. We have prepared and characterized a 19 kDa fucan fraction from brown seaweed, *Ascophyllum nodosum*. Fucan affects the growth of SMCs in a time- and dose-dependent, reversible and non-toxic fashion. As determined by cell counting, [³H]thymidine incorporation, and microcytofluorimetry analysis, heparin was less active than fucan in inhibiting SMC growth. Fucan and heparin act by preferential blocking of G₀/G₁, thus decreasing the G₀/S transition. Binding experiments with [¹²⁵I]fucan indicated saturable, unlabeled-fucan displaceable binding sites with an apparent K_d of 30 nM. Moreover, displacement experiments performed with various polysaccharides revealed that antiproliferative compounds interacted with these membrane sites, but non-antiproliferative polysaccharides (dextran, chondroitin sulfate) did not, providing evidence of a correlation between binding to SMCs and their antiproliferative activity. When cells were exposed at 37 degrees C to a fluorescent 5-([4,6-dichlorotriazin-2-yl]-amino)fluorescein (DTAF)-fucan, internalization occurred and punctate vesicles were observed which accumulated rapidly in the perinuclear region as previously reported for heparin. Nuclear preparations (membranes + contents) of cultured SMCs previously incubated with radiolabeled heparin or fucan indicated the presence of radioactivity, suggesting an antiproliferative action of both polysaccharides at the nuclear level. Collectively, these observations indicated that fucan and heparin share some similar mechanisms of action, such as SMC growth inhibition, binding, and internalization. In the accompanying paper (Logeart et al., Eur. J. Cell Biol. 74, 1997, this issue), we describe the effect of fucans of different molecular weights and conclude that there is no direct link between polysaccharide degradation and the antiproliferative effect on SMCs.

1997

A long and not linear journey

> [Arterioscler Thromb Vasc Biol.](#) 2002 Oct 1;22(10):1604-9.
doi: 10.1161/01.atv.0000032034.91020.0a.

Low molecular weight fucoidan prevents neointimal hyperplasia in rabbit iliac artery in-stent restenosis model

Jean-François Deux ¹, Anne Meddahi-Pellé, Alain F Le Blanche, Laurent J Feldman, Sylvia Collicec-Jouault, Françoise Brée, Frank Boudghène, Jean-Baptiste Michel, Didier Letourneur

Affiliations + expand

PMID: 12377737 DOI: [10.1161/01.atv.0000032034.91020.0a](#)

2002

Abstract

Objective: Smooth muscle cell (SMC) proliferation within the intima is regulated by heparan sulfates. We studied a low molecular weight (LMW) fucoidan (sulfated polysaccharide from brown seaweed) on SMC proliferation in vitro and intimal hyperplasia in vivo.

Methods and results: In vitro study revealed that LMW fucoidan reduces rabbit SMC proliferation and is internalized in SMC perinuclear vesicles. On rabbit iliac arteries perfused in vivo with fluorolabeled LMW fucoidan after angioplasty, the labeling was mainly located on sites of injury. Pharmacokinetic studies showed that LMW fucoidan exhibited in rats an elimination half-life of 56+/-25 minutes (n=8) after intravenous administration and a constant plasma rate for > or =6 hours after intramuscular administration. After stent implantation in their iliac arteries, rabbits were also treated with LMW fucoidan (5 mg/kg IM twice a day). Histomorphometric analysis at day 14 indicated that LMW fucoidan reduced intimal hyperplasia by 59% (1.79+/-0.4 versus 0.73+/-0.2 mm², P<0.0001) and luminal cross-sectional area narrowing by 58% (0.38+/-0.08 versus 0.16+/-0.04, P<0.0001). Blood samples showed no anticoagulant activity due to LMW fucoidan.

Conclusions: This natural polysaccharide with high affinity for SMCs and sustained plasma concentration markedly reduced intimal hyperplasia, suggesting its use for the prevention of human in-stent restenosis.

And then ...

Comparative Study > *Biochim Biophys Acta*. 2009 Feb;1790(2):141-6.

doi: 10.1016/j.bbagen.2008.10.008. Epub 2008 Nov 5.

Affinity of low molecular weight fucoidan for P-selectin triggers its binding to activated human platelets

Laure Bachelet ¹, Isabelle Bertholon, Damien Lavigne, Roger Vassy, Martine Jandrot-Perrus, Frédéric Chaubet, Didier Letourneur

Affiliations + expand

PMID: 19026722 DOI: 10.1016/j.bbagen.2008.10.008

Abstract

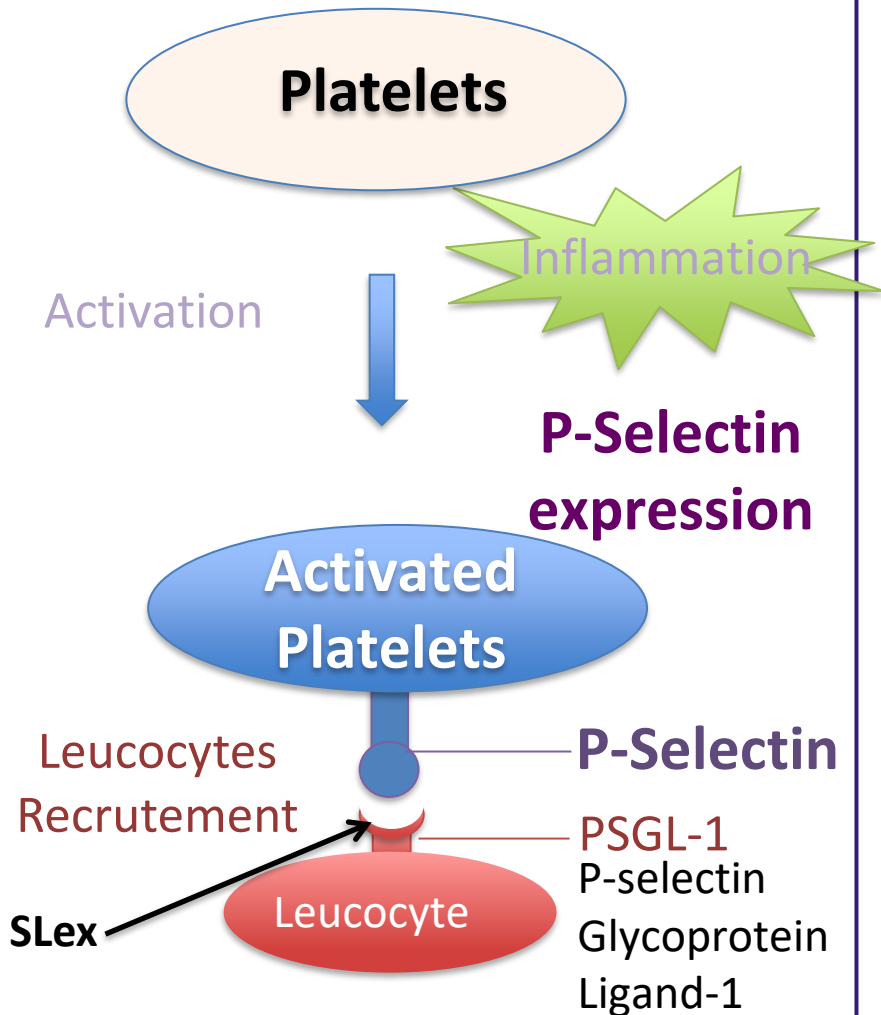
Background: P-selectin is an adhesion receptor expressed on activated platelets and endothelial cells. Its natural ligand, P-selectin glycoprotein ligand-1, is expressed on leucocytes and the P-selectin/PSGL-1 interaction is involved in leukocyte rolling. We have compared the interaction of P-selectin with several low molecular weight polysaccharides: fucoidan, heparin and dextran sulfate.

Methods: Binding assays were obtained from the interaction of the polysaccharides with Sialyl Lewis X and PSGL-1 based constructs onto microtiter plates coated with P-selectin. SELDI TOF mass spectrometry was performed with anionic chips arrays coated with P-selectin in the absence or in the presence of polysaccharides. K_d were obtained from surface plasmon resonance experiments with immobilized P-selectin constructs, polysaccharides being injected in the mobile phase. Human whole blood flow cytometry experiments were performed with fluorescein isothiocyanate labelled polysaccharides with or without platelets activators.

Results: The fucoidan prevented P-selectin binding to Sialyl Lewis X with an IC_{50} of 20 nM as compared to 400 nM for heparin and <25000 nM for dextran sulfate. It exhibited the highest affinity for immobilized P-selectin with a K_D of 1.2 nM, two orders of magnitude greater than the $K(D)$ of the other polysaccharides. Mass spectrometry evidenced the formation of a complex between P-selectin and fucoidan. The intensity of the fucoidan binding to platelets was dependent on the level of platelet activation. Competition between fucoidan and an anti P-selectin antibody demonstrated the specificity of the interaction.

2009

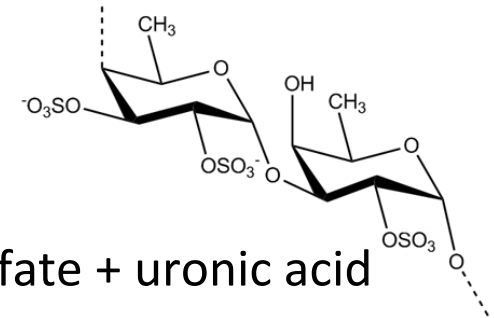
P-Selectin



Fucoidan : Mimic of SLex Ligand of P-Selectin



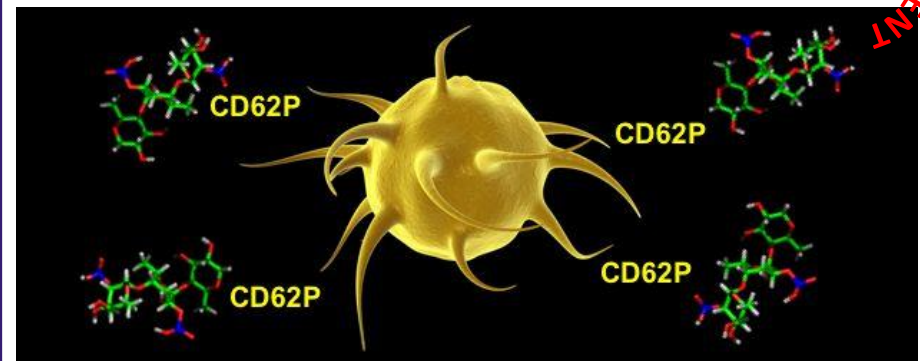
Natural Polysaccharide



Fucose + sulfate + uronic acid

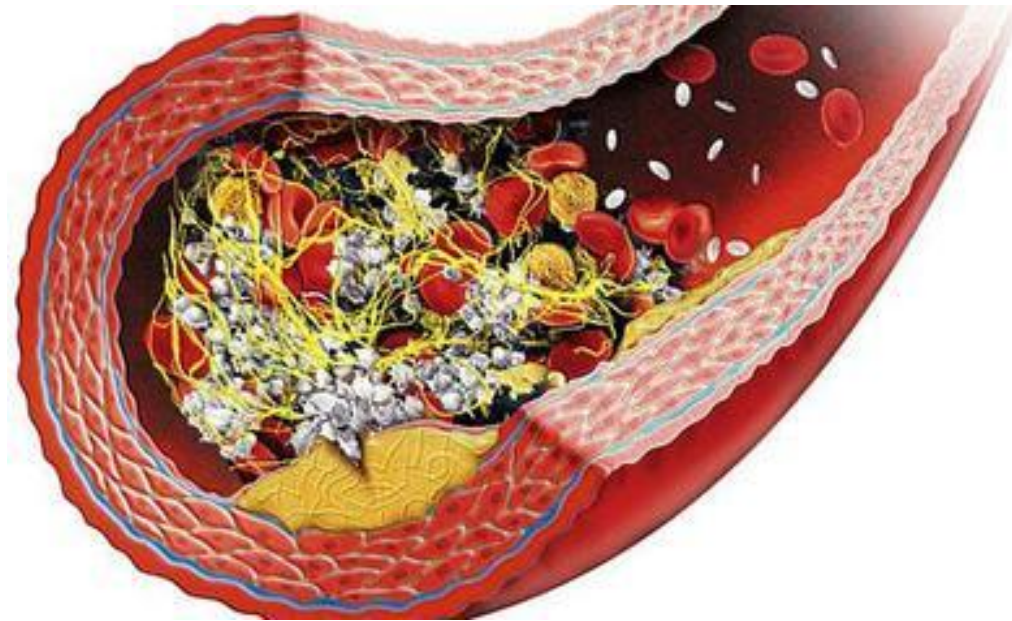
P-Selectin (CD 62P) interactions
in vitro & *in vivo*

L. Bachelet et al., BBA (2009) + Patent (2009)



P-Selectin (CD 62P) also present on activated Endothelium

Thrombus Detection in Clinic ?



(19) **United States**

(12) **Patent Application Publication**
Michel et al.

(10) **Pub. No.:** US 2012/0093725 A1

(43) **Pub. Date:** Apr. 19, 2012

(54) **FUCOIDANS AS LIGANDS FOR THE
DIAGNOSIS OF DEGENERATIVE
PATHOLOGIES**

(75) **Inventors:** Jean-Baptiste Michel, Paris Cedex
(FR); Didier Letourneur, Paris
Cedex (FR); Frederic Chaubet,
Paris Cedex (FR); Laure Bachelet,
Paris Cedex (FR); Francois Rouzet,
Paris Cedex (FR); Alain

A61P 9/10 (2006.01)

A61P 25/00 (2006.01)

G01N 21/78 (2006.01)

A61P 35/00 (2006.01)

A61P 35/04 (2006.01)

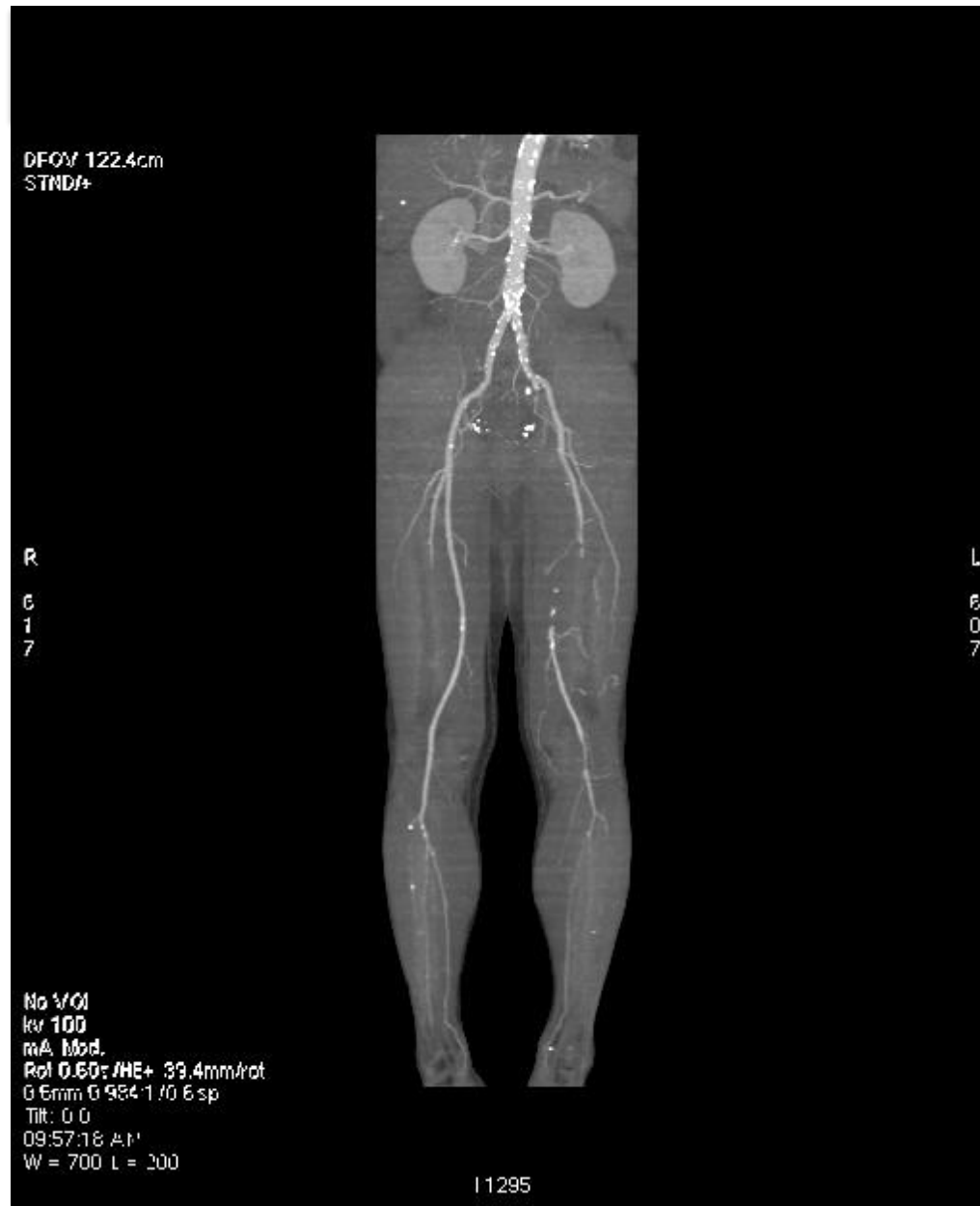
A61P 29/00 (2006.01)

G01N 33/82 (2006.01)

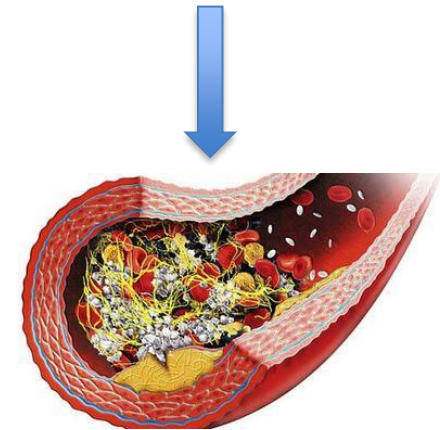
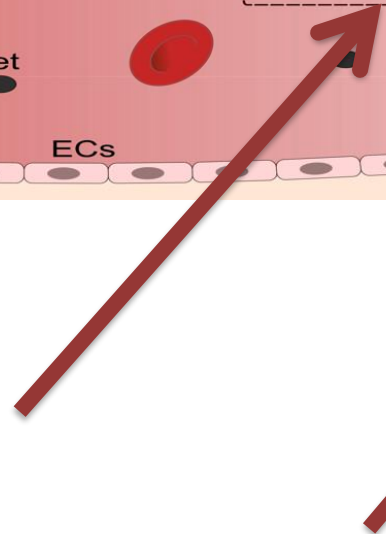
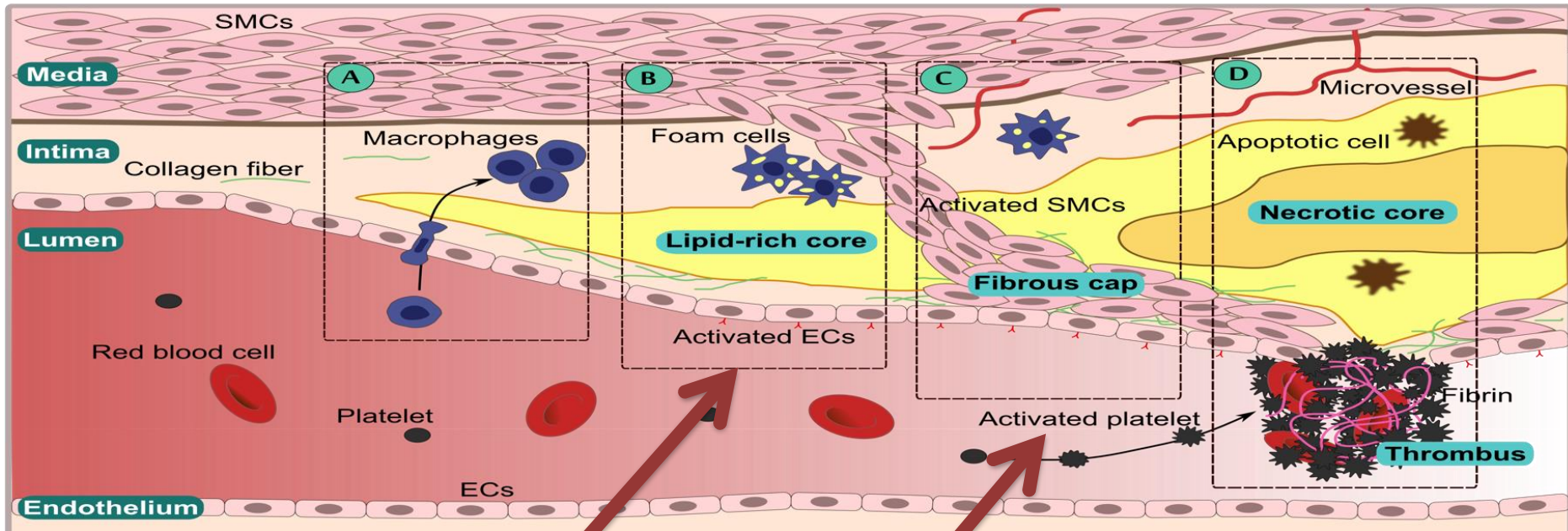
C07F 13/00 (2006.01)

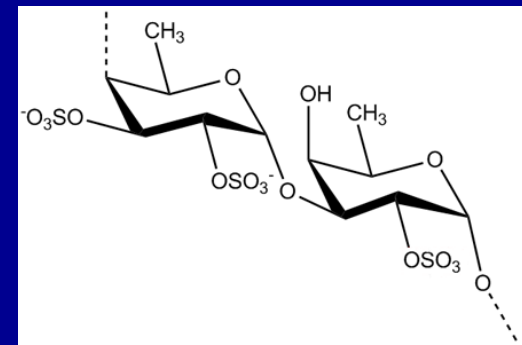
A61P 25/28 (2006.01)

Thrombus Detection in Humans

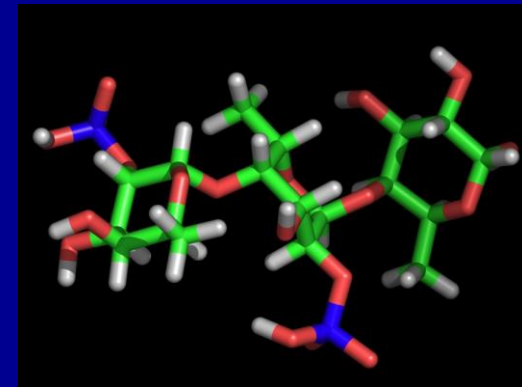


Strategy for Early Detection of Thrombus





Fucoidan : sulfated polyfucose



2015 : Agreement for LMW fucoidans
=> Pharmaceutical use ingredient (ANSM)



Solabia prend le large avec l'acquisition d'Algues & Mer

13 novembre 2016

PARTAGER :



Le groupe **Solabia**, fournisseur français d'ingrédients cosmétiques issus des biotechnologies (fermentation et biocatalyse enzymatique), de la chimie fine et des technologies d'extractions végétales, complète son offre en capitalisant sur la richesse et la diversité des algues via l'acquisition de la société **Algues & Mer**, une société créée en 1994 et dont le siège est situé sur l'île d'Ouessant, en mer d'Iroise où elle bénéficie de conditions de sourcing exceptionnelles.



L'île d'Ouessant présente une grande variété de peuplements d'algues sauvages ou cultivées. - Crédit photo : Vuldendive

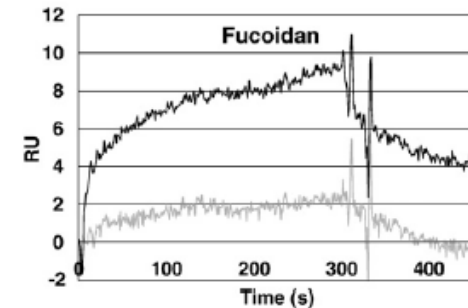
2016

Biacore : Binding affinity for P-selectin

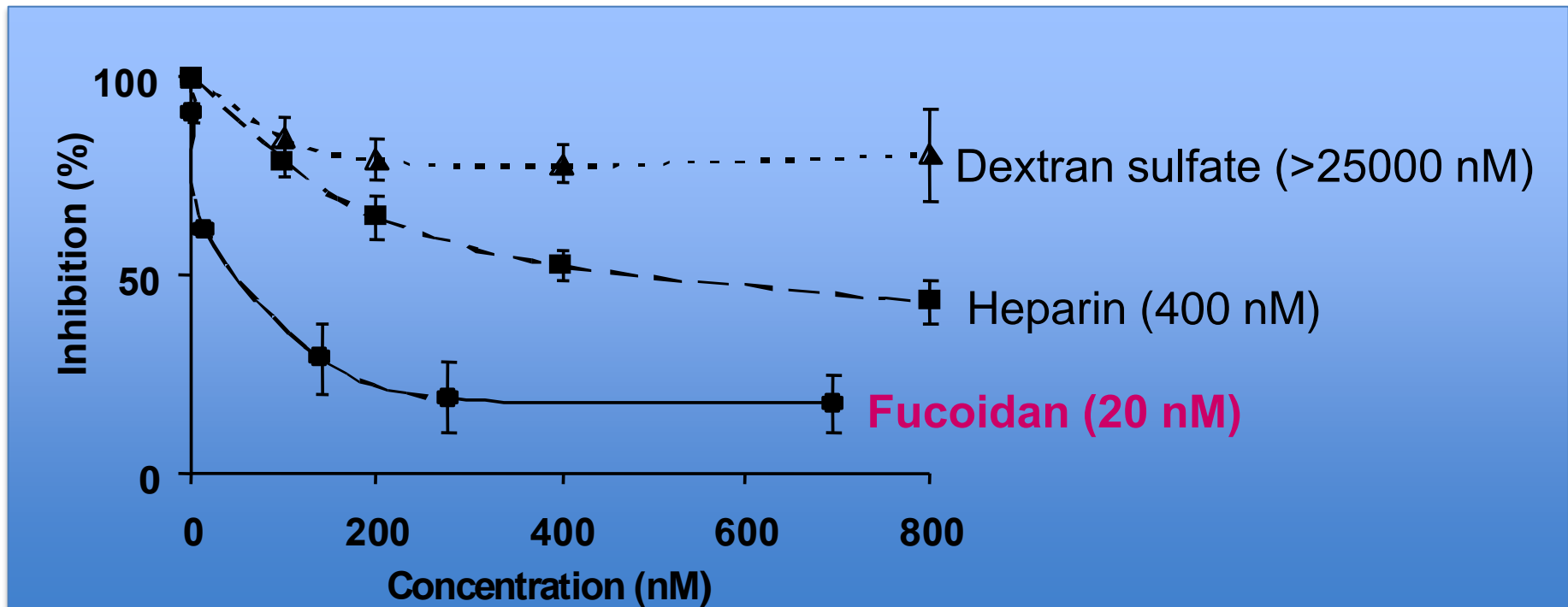
Fucoidan
 $K_D = 1.2 \text{ nM}$

Dextran sulfate
 $K_D = 120 \text{ nM}$

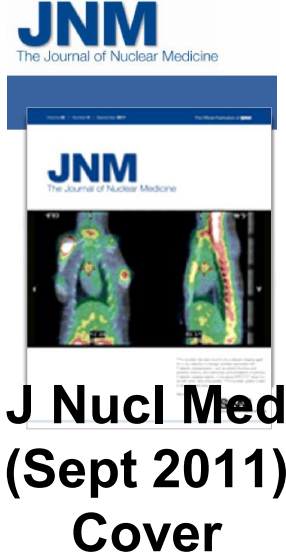
Heparin
 $K_D = 780 \text{ nM}$



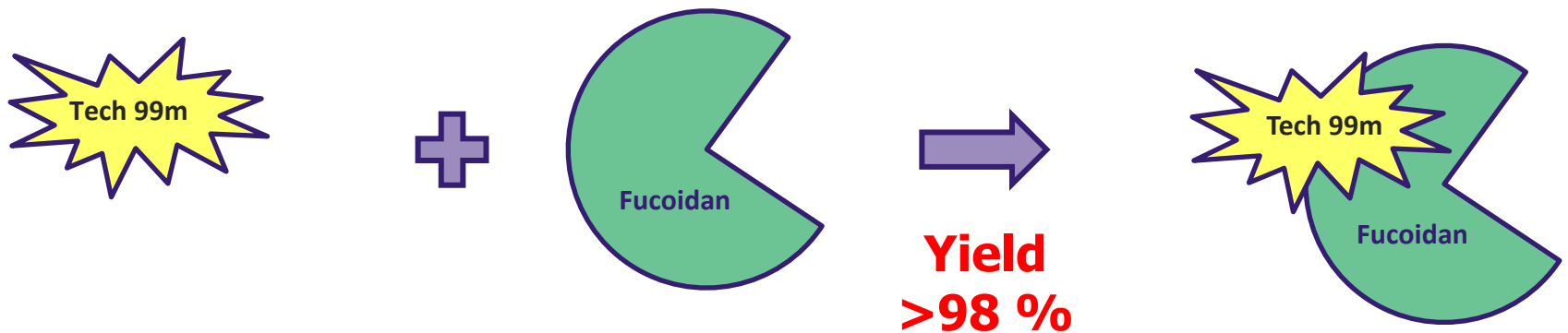
ELISA : Fucoidan displacement of Sle^x on P-selectin



Fucoidan for SPECT *In vivo*



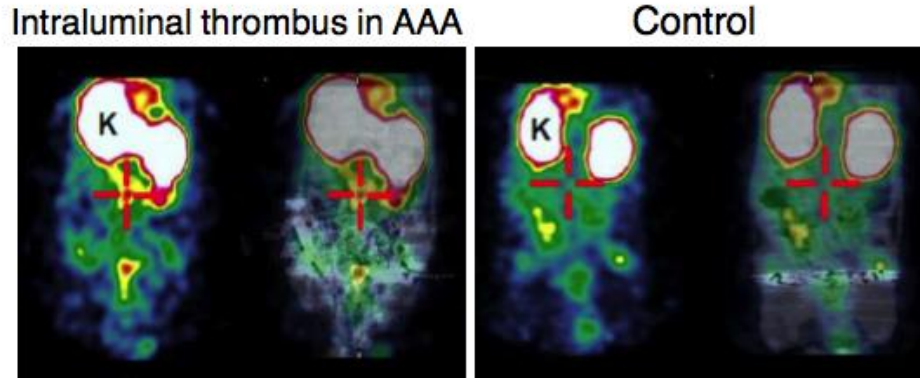
99m Technetium + Fucoidan



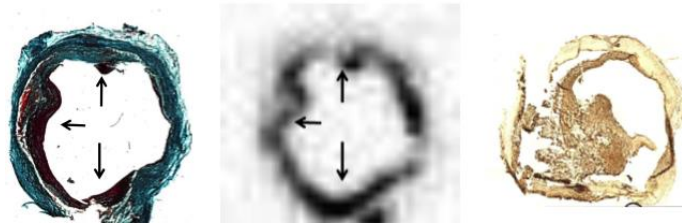
Detection of thrombus with 99mTc-fucoidan by SPECT

Intraluminal Thrombus in rat Abdominal Aorta Aneurysm SPECT/CT in AAA and control

In vivo

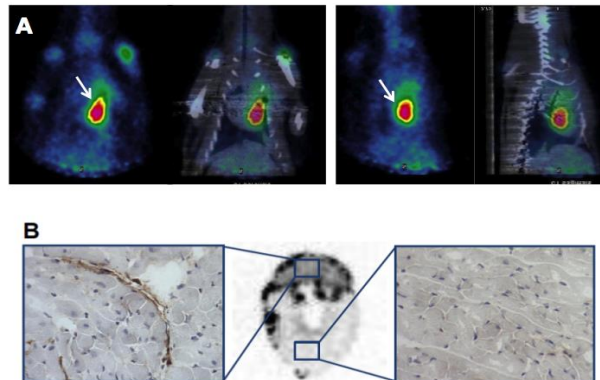


Ex vivo/histology



Ischemia-reperfusion

Transient occlusion of the left anterior descending coronary artery in rat



J Nucl Med
(Sept 2011)
Cover

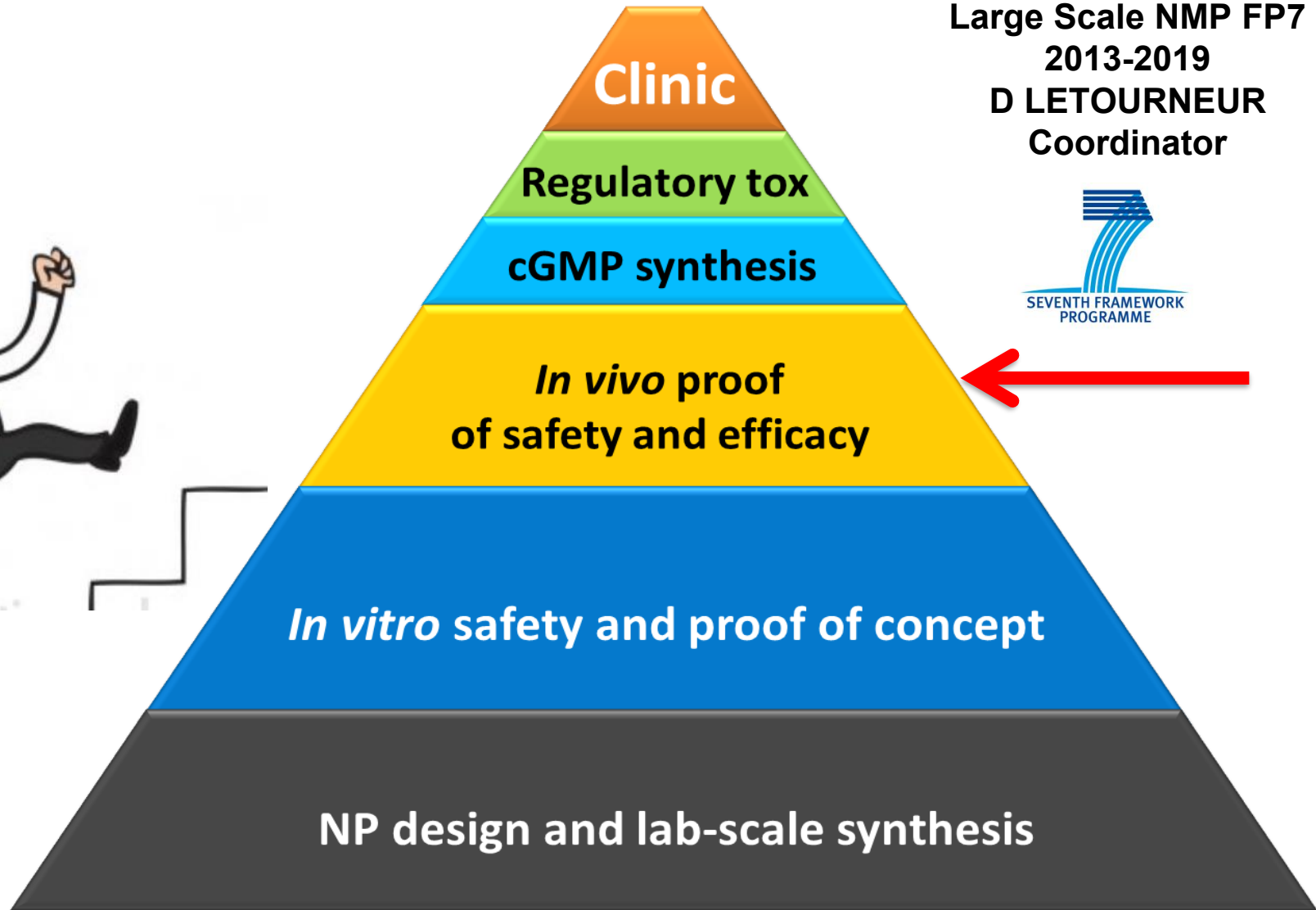
JNM
The Journal of Nuclear Medicine



Endocarditis

Toward the Clinical Thrombus Imaging with a GMP-Grade Fucoïdan

Large Scale NMP FP7
2013-2019
D LETOURNEUR
Coordinator



Toward the Clinical Thrombus Imaging with a GMP-Grade Polysaccharide

Candidate selection criteria



Product physicochemistry

- Size
- PDI
- Zeta-potential
- Activity (if active ingredient)

Ingredient quality

- GRAS Ingredient
- Known toxicity?
- Degradation products
- Sterility/Pyrogenicity

Manufacturability

- Scalability
- Robustness of process
- Costs of goods

Stability

- Stability on storage

Toxicity

- Biocompatibility
- Hemocompatibility
- Immunogenicity

Pharmacokinetics

- Biodistribution
- Elimination
- ADME

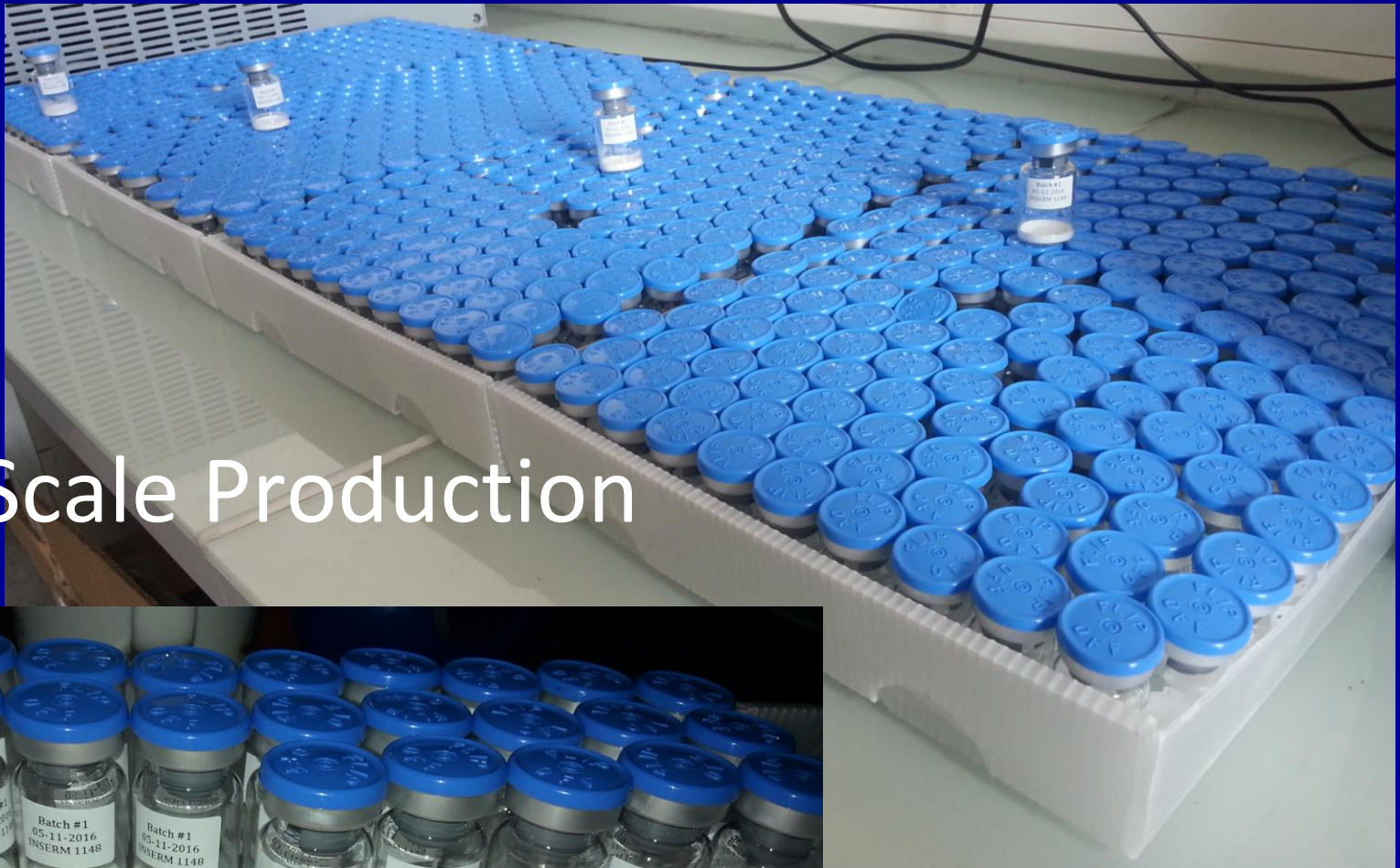
Efficacy

- Passive or active targeting
- Equivalent/better than standard
- Reduced side effects
- Reduced dosing

I. Cicha *et al*,

Cardiovasc Res 2018

Clinical Thrombus Imaging with a GMP-Grade Polysaccharide



Lab Scale Production

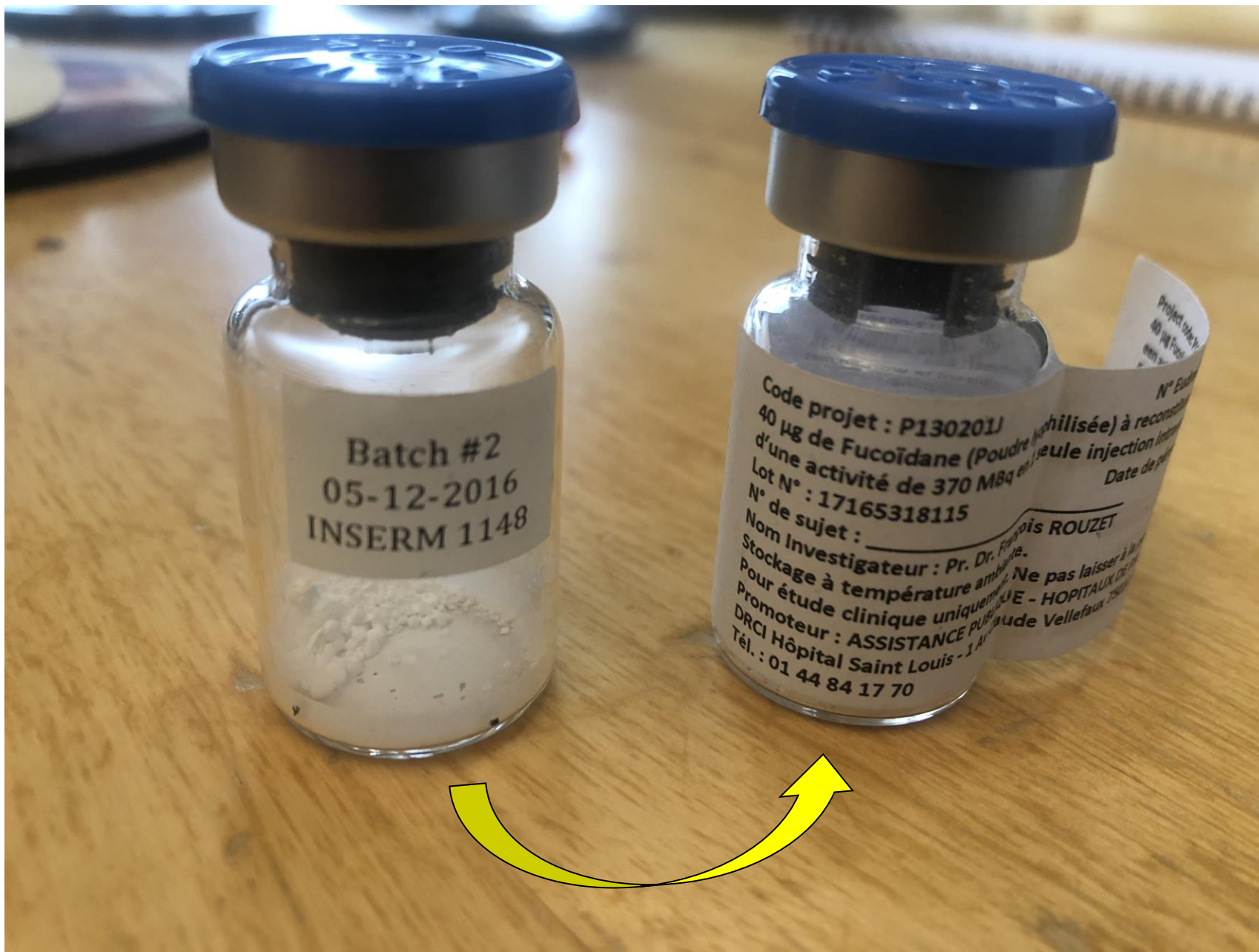




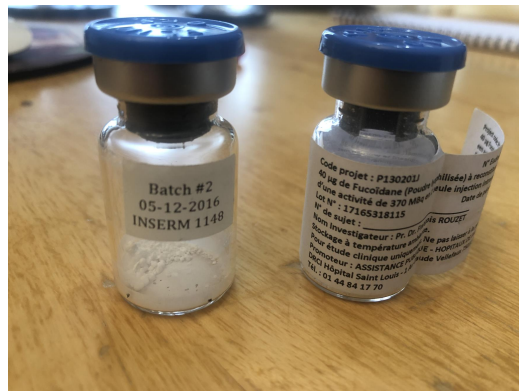
GMP manufacturing process of fucoidan for SPECT imaging



GMP Fucoidan for Molecular Imaging








GMP Fucoidan for Molecular Imaging



Article

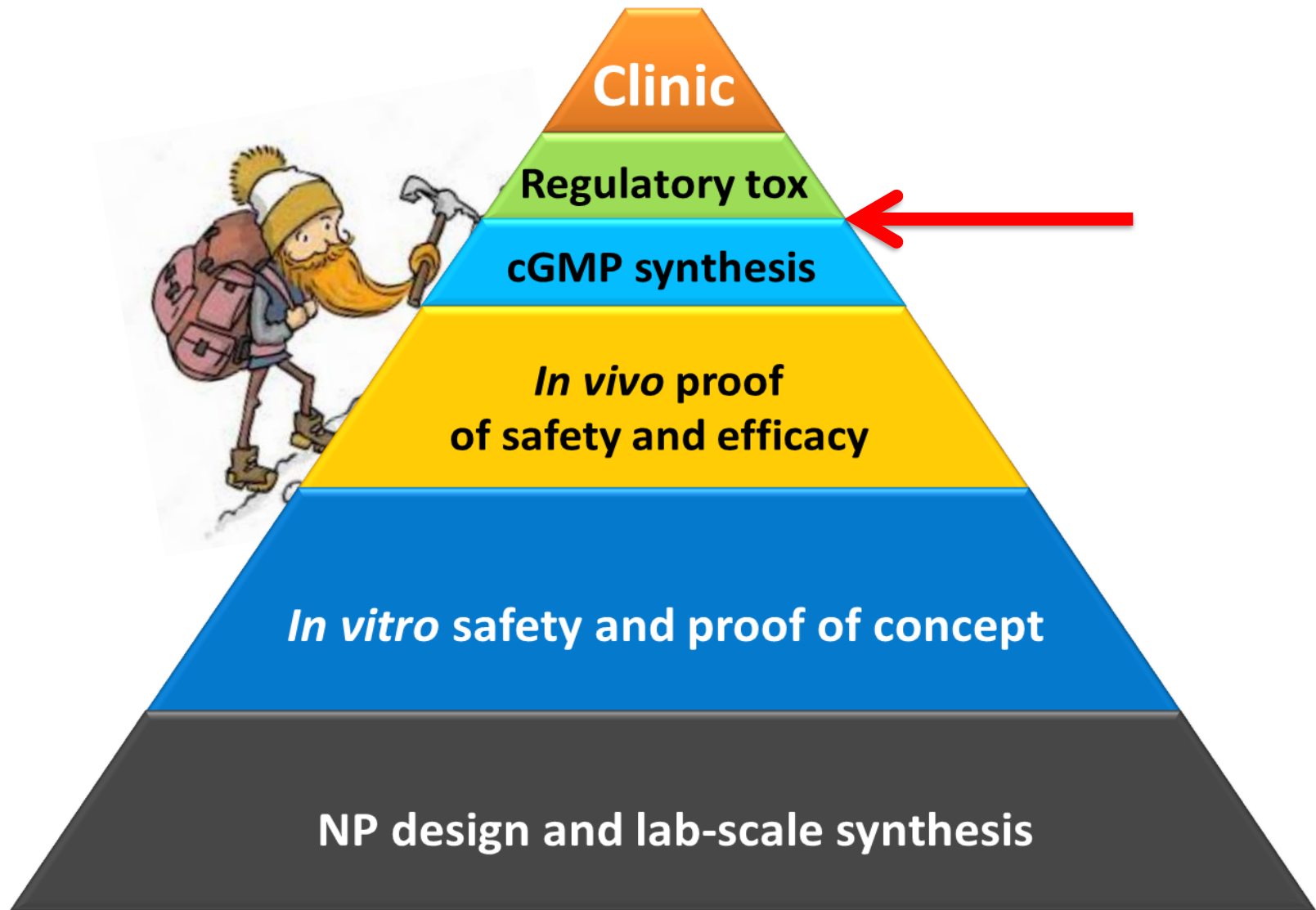
Pharmaceutical Development and Safety Evaluation of a GMP-Grade Fucoidan for Molecular Diagnosis of Cardiovascular Diseases

Cédric Chauvierre ^{1,*} , Rachida Aid-Launais ^{1,2}, Joël Aerts ^{2,3}, Frédéric Chaubet ¹ , Murielle Maire ¹, Lucas Chollet ^{1,4}, Lydia Rolland ⁴, Roberta Bonafé ⁵, Silvia Rossi ⁵, Simona Bussi ⁵ , Claudia Cabella ⁵, Laszlo Dézsi ⁶, Tamas Fülöp ⁶, Janos Szebeni ⁶, Youssef Chahid ⁷, Kang H. Zheng ⁷, Erik S. G. Stroes ⁷, Dominique Le Guludec ^{1,2,3}, François Rouzet ^{1,2,3}  and Didier Letourneur ¹ 

Mar. Drugs **2019**, *17*, 699; doi:10.3390/md17120699

2019

Toward the Clinical Thrombus Imaging with a GMP-Grade Fucoidan



CdS227. Extended single dose toxicity study of fucoidan extract formulation after intravenous administration to rats.

FINAL REPORT

⇒ **No toxicity until the maximum tested dose equivalent to 20 mg (for 50 kg bw)**

Max injected dose in human : 40 µg per patient

> 500 x for the safety range

Product Name: Fucoidan extract
Code and Study Number: CdS227
Study Director: Silvia Rossi

Sponsor:
Inserm -Unité de Recherche UMRS1148
CHU X. Bichat, 46 rue Henri Huchard
75018 Paris, France

Document ID: BIM-TDC-AF4A01.17-R-Bracco

No animals died during the study, and no clinical signs or treatment related changes in body weight or body weight gain were observed in all animals treated with fucoidan extract formulation up to 400 µg/kg.

No treatment related changes in hematology, blood chemistry, coagulation and urinalysis parameters were observed.

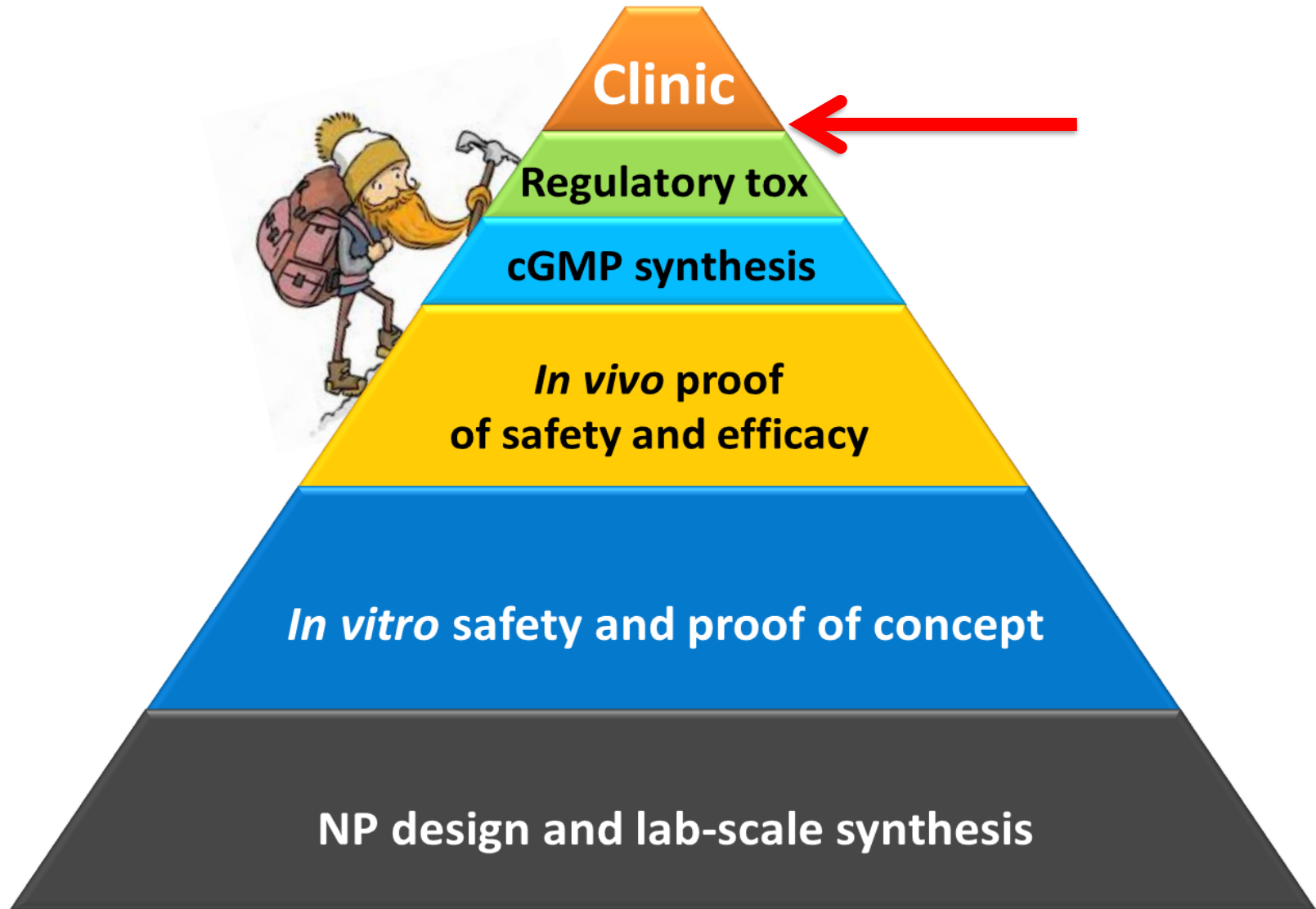
No treatment related changes in absolute and relative organ weights were observed.

No fucoidan extract-related microscopic findings were observed at histopathology examination.

In conclusion, the No Observed Adverse Effect Level (NOAEL) for fucoidan extract formulation after a single intravenous administration to rats is 400 µg/kg.

Regulatory Toxicity of GMP fucoidan

Toward the Clinical Thrombus Imaging with a GMP-Grade Polysaccharide



Fucoidan: submission IMPD + IB



**LVTS
INSERM
U1148**

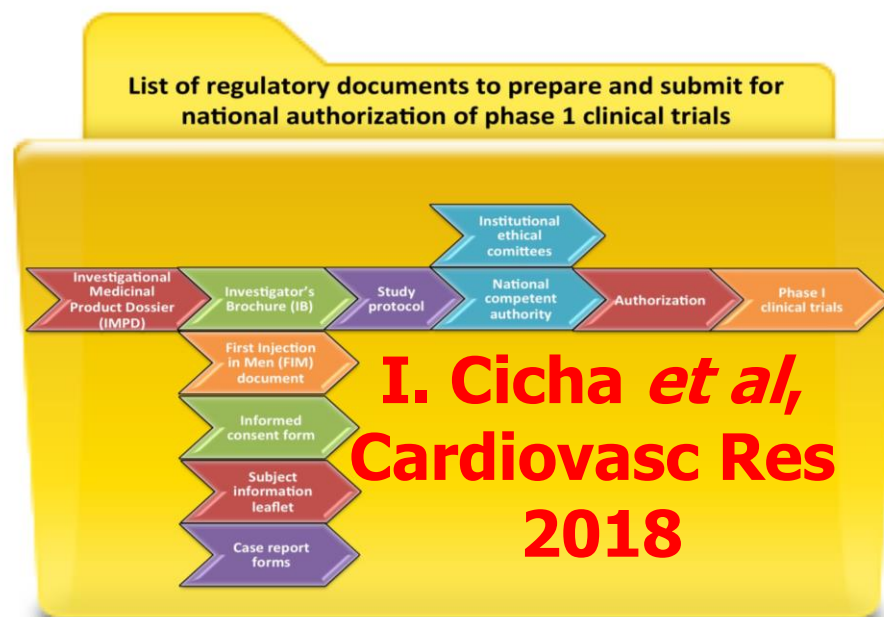
13DLC-Nanoathero_ lettre2_ autorisation-utilisation-IB_20170912_MDH - CC.pdf	Portable Document Format File	25 kb
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13DLC-Nanoathero_Formulaire demande AEC initiale ANSM_20171117_MDH.pdf	Portable Document Format File	707 kb
13DLC-Nanoathero_nifc-v1.0_20171113_DRICI.pdf	Portable Document Format File	133 kb
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Nanoathero-Tab-FIM_v1-0_20171115 Finale.pdf	Portable Document Format File	45 kb
Algues & Mer certificate bio CER-OPT85075-C131593.pdf	Portable Document Format File	243 kb
LabelGenerator_v8 - FucoTc V1.pdf	Portable Document Format File	202 kb
AMATSI DBI autorisation M17_020.pdf	Portable Document Format File	1346 kb
AMATSIGROUP IDRON GMP certificate Ansm med exp HPF-FR-036-2017.pdf	Portable Document Format File	146 kb
GMO-free certificate FUCO Oct.17.pdf	Portable Document Format File	292 kb
IMPD_Inserm_2017_32P_fucoidane reconstitué marqué_final_27-oct.pdf	Portable Document Format File	2758 kb
IMPD_Inserm_2017_32S_32P_fucoidane lyophilisat_Final 19_OCT2017.pdf	Portable Document Format File	2332 kb

Fucoidan: submission IMPD + IB



**INSERM
U1148**

13DLC-Nanoathero_ lettre2_ autorisation-utilisation-IB_20170912_MDH - CC.pdf	Portable Document Format File	25 kb
13DLC-Nanoathero_Brochure Investigateur (BI)_V4.0_201711109.pdf	Portable Document Format File	2887 kb
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13DLC-Nanoathero_nifc-v1.0_20171117_MDH.pdf	Portable Document Format File	33 kb
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13DLC-Nanoathero_Résumé-Projet de phase I.pdf	Portable Document Format File	40 kb
2017-001015-36 FR 20171116 C	Portable Document Format File	9 kb
bichatradiopharmacie2005[50859].pdf	Portable Document Format File	21 kb
CourrierDemande Initiale-AEC-Phase I.pdf	Portable Document Format File	98 kb
Nanoathero-Tab-FIM_v1-0_20171117_MDH.pdf	Portable Document Format File	5 kb
Algues & Mer certificate bio CEI.pdf	Portable Document Format File	43 kb
LabelGenerator_v8 - FucoTe V1.0_20171117_MDH.pdf	Portable Document Format File	02 kb
AMATSI DBI autorisation M17_20171117_MDH.pdf	Portable Document Format File	346 kb
AMATSIGROUP IDRON GMP certificate Ansm med exp HPF-FR-036-2017.pdf	Portable Document Format File	146 kb
GMO-free certificate FUCO Oct.17.pdf	Portable Document Format File	292 kb
IMPD_Inserm_2017_32P_fucoidane reconstitué marqué_final_27-oct.pdf	Portable Document Format File	2758 kb
IMPD_Inserm_2017_32S_32P_fucoidane lyophilisat_Final 19_OCT2017.pdf	Portable Document Format File	2332 kb



Fucoidan: submission IMPD + IB



13DLC-Nanoathero_lettre2_autorisation-utilisation-IB_20170912_MDH - CC.pdf

Portable Document Format File 25 kb



ESC

European Society of Cardiology

Cardiovascular Research (2018) **114**, 1714–1727

doi:10.1093/cvr/cvy219

REVIEW

2018

From design to the clinic: practical guidelines for translating cardiovascular nanomedicine

Iwona Cicha^{1*}, Cédric Chauvierre², Isabelle Texier³, Claudia Cabella⁴, Josbert M. Metselaar⁵, János Szebeni⁶, László Dézsi⁶, Christoph Alexiou¹, François Rouzet^{2,7}, Gert Storm^{8,9}, Erik Stroes¹⁰, Donald Bruce¹¹, Neil MacRitchie¹², Pasquale Maffia^{12,13,14}, and Didier Letourneur^{2*}

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IMPD_Inserm_2017_32P_fucoidane reconstitué marqué_final_27-oct.pdf

Portable Document Format File 2758 kb

IMPD_Inserm_2017_32S_32P_fucoidane lyophilisat_Final 19_OCT2017.pdf

Portable Document Format File 2332 kb



SEVENTH FRAMEWORK PROGRAMME

NanoAthero

Phase I Clinical Thrombus Imaging with a GMP-Grade Fucoïdan

19/01/2018 09:29 +33155873492 ANSM/BIOVA PAGE 01/02

ansm
Agence nationale de sécurité du médicament et des produits de santé

AUTORISATION D'ESSAI CLINIQUE DE MEDICAMENT A USAGE HUMAIN

Nombre de pages : 1
(incluant la page de garde)

Envoi par Télécopie Date : 17-01-2018

Identifiants de l'essai clinique			
Titre	Nanothero : Nanomedicine for target-specific imaging and treatment of atherosclerosis: development and initial clinical feasibility NANOATHERO :Etude de la tolérance, de la biodistribution et de la dosimétrie du Fucoïdane radiomarqué au Technétium-99m		
Promoteur	ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS (AP-HP)	Réf. CPP	Code 23
Réf. Promoteur	P130201J (NANOATHERO)	N° EudraCT	2017-001015-36
		Réf. ANSM	170726A-13
Expéditeur		Destinataire (demandeur : nom / société / tél.)	
ANSM / Direction des médicaments en oncologie, hématologie, immunologie et néphrologie Pôle Oncologie solide		Florence Favrel Feuillade (01 44 84 17 70) DRCI Hôpital Saint Louis 1 avenue Claude Vellefaux 75010 Paris	
Dossier suivi par : Caroline FEDRIGO Tél : 33 (0) 1 55 87 41 88 / 34 63 - Fax : 33 (0) 1 55 87 34 52 Mel : aec-essaiscliniques@ansm.sante.fr		Fax 01 44 84 17 01	
CPP destinataire en copie	EST I	Fax	03 80 42 54 86
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AEC

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Vu les compléments versés par le promoteur en date du 16/01/2018 et notamment le protocole de l'essai cité en objet modifié (version 1.1 datée du 15 janvier 2018), suite à la demande de l'ANSM ;

L'autorisation mentionnée à l'article L. 1123-8 du code de la santé publique est accordée pour l'essai clinique cité en objet.

La Chef produits
Hémovigilance, produits sanguins labiles
thérapie cellulaire et produits radiopharmaceutiques
Isabelle SALETTE-MARIE

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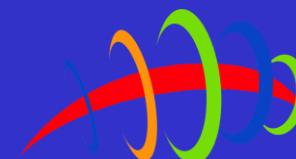
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143/147, bd Anatole France - F-93285 Saint-Denis cedex - tél. +33 (0) 1 55 87 30 00 - www.ansm.sante.fr Page 1 sur 1

**ANSM agreement
January 17, 2018
(France)**



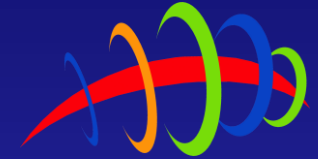
**LVTS
INSERM U1148**



Phase I Clinical Thrombus Imaging with a GMP-Grade Fucoïdan



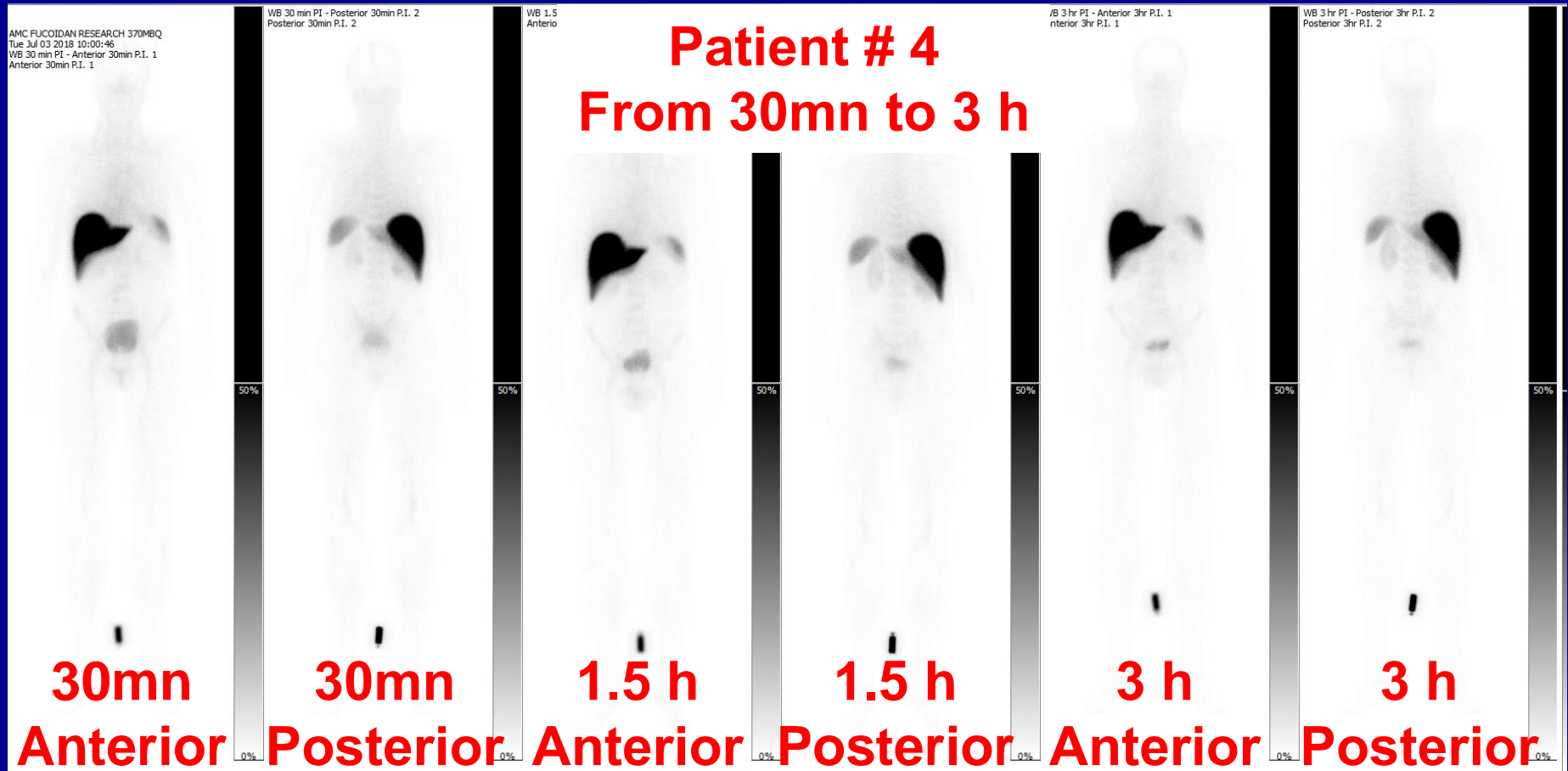
LVTS
INSERM U1148



**Dutch
agreement
March 8, 2018**

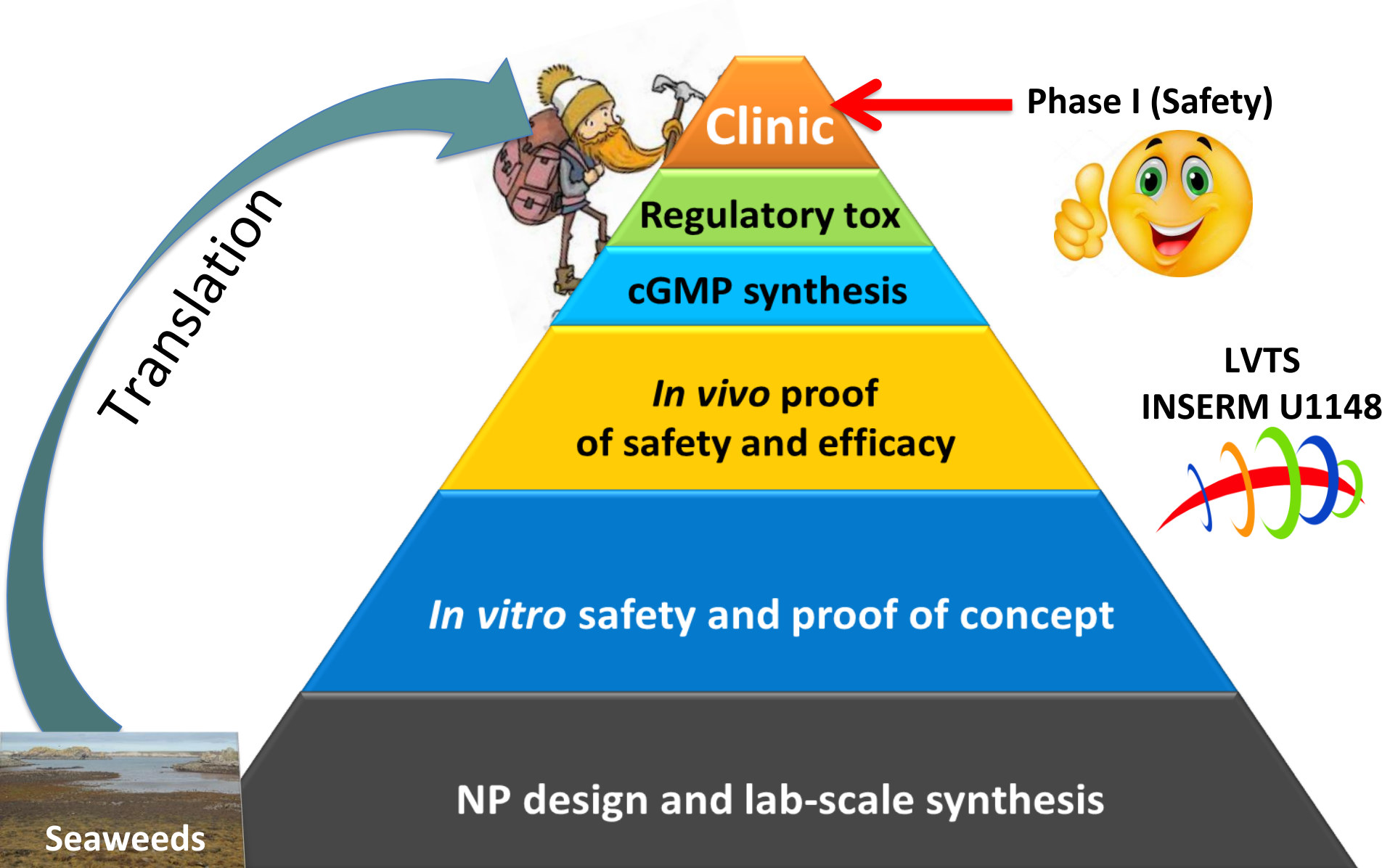
**Clinical trial (Phase I) started in 2018 at AMC,
Amsterdam (NL)**

Phase I - Clinical Thrombus Imaging with a GMP-Grade Fucoidan



Phase I completed in 2018 :
10 patients - no side effect, usual uptake

The Clinical Thrombus Imaging with a GMP-Grade Fucoïdan



The Clinical Thrombus Imaging Phase IIa with a GMP-Grade Fucoidan



Aan de heer prof.dr. E.S.G. Stroes
Inwendige geneeskunde
F4-211

Medisch Ethische Toetsingscommissie AMC
XT4-148
telefoon: 020 56 67389

Amsterdam, 9 mei 2019
ons kenmerk: 2019_032#B2019322
betreft: **Goedkeuring Raad van Bestuur: 2019_032 / NL68750.018.19**
A proof-of-concept study to evaluatie 99mTechnetium radiolabelled Fucoidan as diagnostic modality for thrombosis

Geachte heer Stroes,

Hierbij laat ik u weten dat de Raad van Bestuur van het AMC kennis heeft genomen van bovengenoemd onderzoeksprotocol.

De Raad van Bestuur van het AMC geeft u hierbij haar goedkeuring dit onderzoek uit te voeren in het AMC gelet op

- het positieve oordeel van de beoordelende commissie voor uitvoering van dit protocol in het AMC,
- de AMC appendix,
- de verklaring van geen bezwaar van de bevoegde instantie, CCMO.

De Raad van Bestuur dient op de hoogte te zijn van het beloop van al het wetenschappelijk onderzoek in het AMC. Om die reden wordt u gevraagd de volgende gegevens te melden via het e-mailadres mecamc@amc.nl:

- **startdatum** in Nederland = datum eerste inclusie in Nederland
- **einddatum** = datum laatste contact met een proefpersoon; daarbij dient te worden gemeld hoeveel proefpersonen in totaal zijn geïncludeerd
- **tijdelijke opschorting** van de uitvoering: Indien er tijdens het wetenschappelijk onderzoek gegronde redenen zijn om aan te nemen dat voortzetting van het wetenschappelijk onderzoek zou leiden tot onaanvaardbare risico's voor de proefpersoon, schort u de uitvoering van het onderzoek op. Dit moet terstond gemeld worden onder opgave van reden aan het secretariaat van de METC AMC via het e-mailadres mecamc@amc.nl of telefonisch en aan de Raad van Bestuur. Hervatten van het onderzoek kan pas nadat een nader positief oordeel is verkregen van de beoordelende toetsingscommissie.
- **voortijdige beëindiging** van het onderzoek dient onder opgave van reden binnen 15 kalenderdagen gemeld te worden aan de Raad van Bestuur en aan de beoordelende toetsingscommissie.
- **voortgangsrapportage**: jaarlijks het totaal aantal proefpersonen dat op dat moment is geïncludeerd middels een voortgangsrapportageformulier aan de beoordelende toetsingscommissie.

Daarnaast wordt u tweemaal per jaar gevraagd om een aantal studiegegevens via de tool "**Registratie Mensgebonden Onderzoek (RMO)**" in te vullen en te controleren op juistheid en volledigheid.

Voor de goede orde wijzen wij u op het volgende:

- Al het geneesmiddelenonderzoek moet aangemeld worden bij het AMC Kenniscentrum.
- amendementen van geneesmiddelenonderzoek moeten naast de beoordeling door de toetsingscommissie, nog een extra marginale toets ondergaan door de bevoegde instantie. Zie website CCMO voor meer informatie.

- Al het geneesmiddelenonderzoek, al het hulpmiddelenonderzoek en al het overige WMO-plichtig onderzoek met hoog risico dient onafhankelijk gemonitord te worden door gekwalificeerde monitors. Vanaf 1 januari 2019 geldt deze monitoringverplichting ook voor het overige WMO-plichtig onderzoek met matig risico. Het monitoring beleid voor het overige WMO-plichtig onderzoek met verwaarloosbaar risico wordt nader geformuleerd in 2019.
- De Raad van Bestuur wijst onderzoekers erop dat, conform landelijke afspraken, klinisch onderzoekers verplicht zijn de "Basiscurus Regelgeving en Organisatie van Klinisch onderzoek" (BROK) te doorlopen en het bijbehorende certificaat te behalen. Dit geldt ook voor een eventuele her-certificering. De Raad van Bestuur gaat ervan uit dat indien dit nu nog niet het geval is, het afdelingshoofd ervoor zorgdraagt dat de betrokken klinisch onderzoekers van deze studie maximaal zes maanden na aanvang van de studie aan deze verplichting voldaan hebben.

Wij wensen u veel succes bij de uitvoering van dit onderzoek.

Met vriendelijke groet,
De Raad van Bestuur AMC

Prof.dr. A.A. Romijn
Voorzitter

c.c. pdf per e-mail Y.Kaiser

Phase IIa Approval for Deep Vein Thrombosis Amsterdam, May 2019

Clinical trial is ongoing

The Clinical Thrombus Imaging Phase IIa with a GMP-Grade Fucoidan



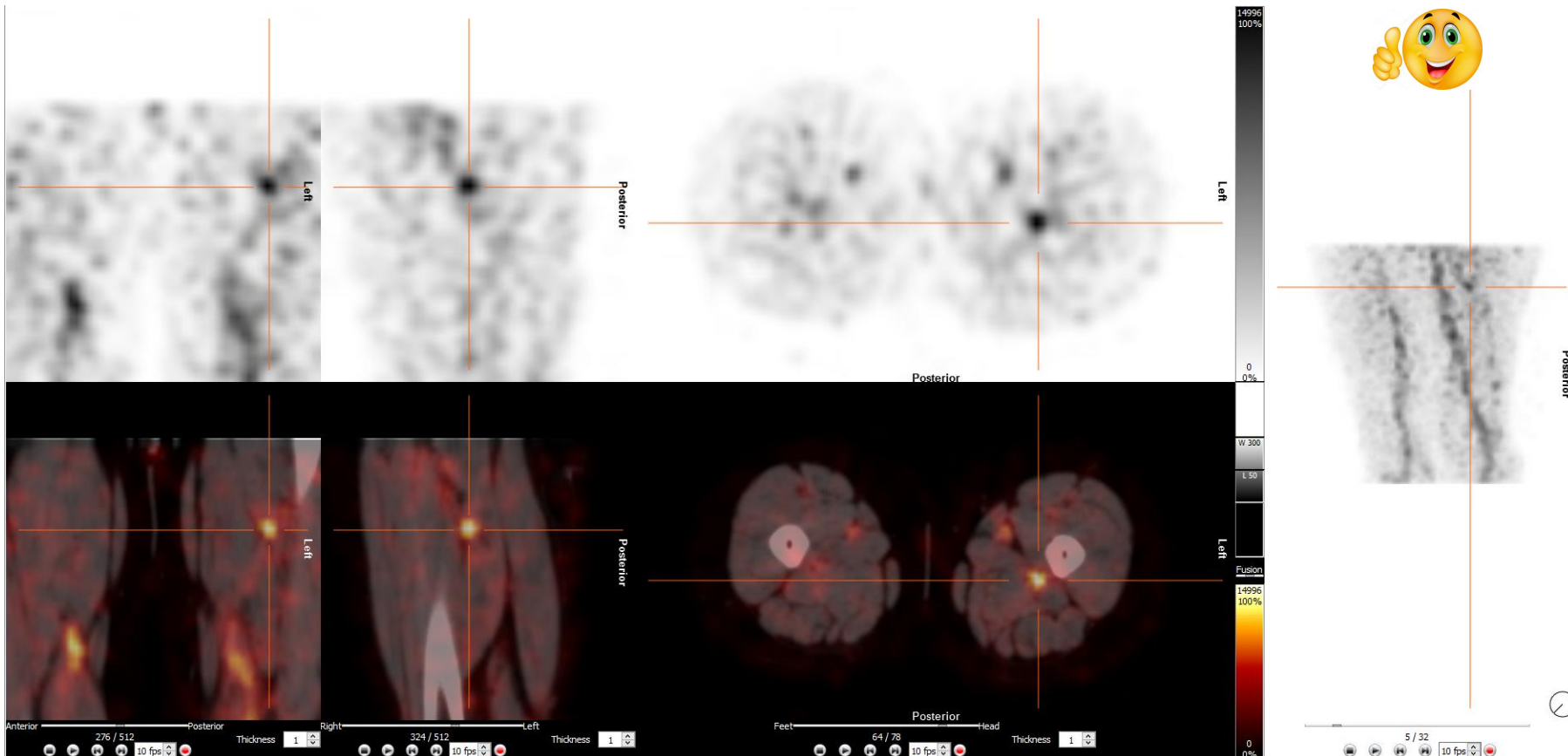
**Amsterdam
November 2019**

**First patient in Phase IIa :
First detection of
Deep Vein Thrombosis
with Fucoidan**

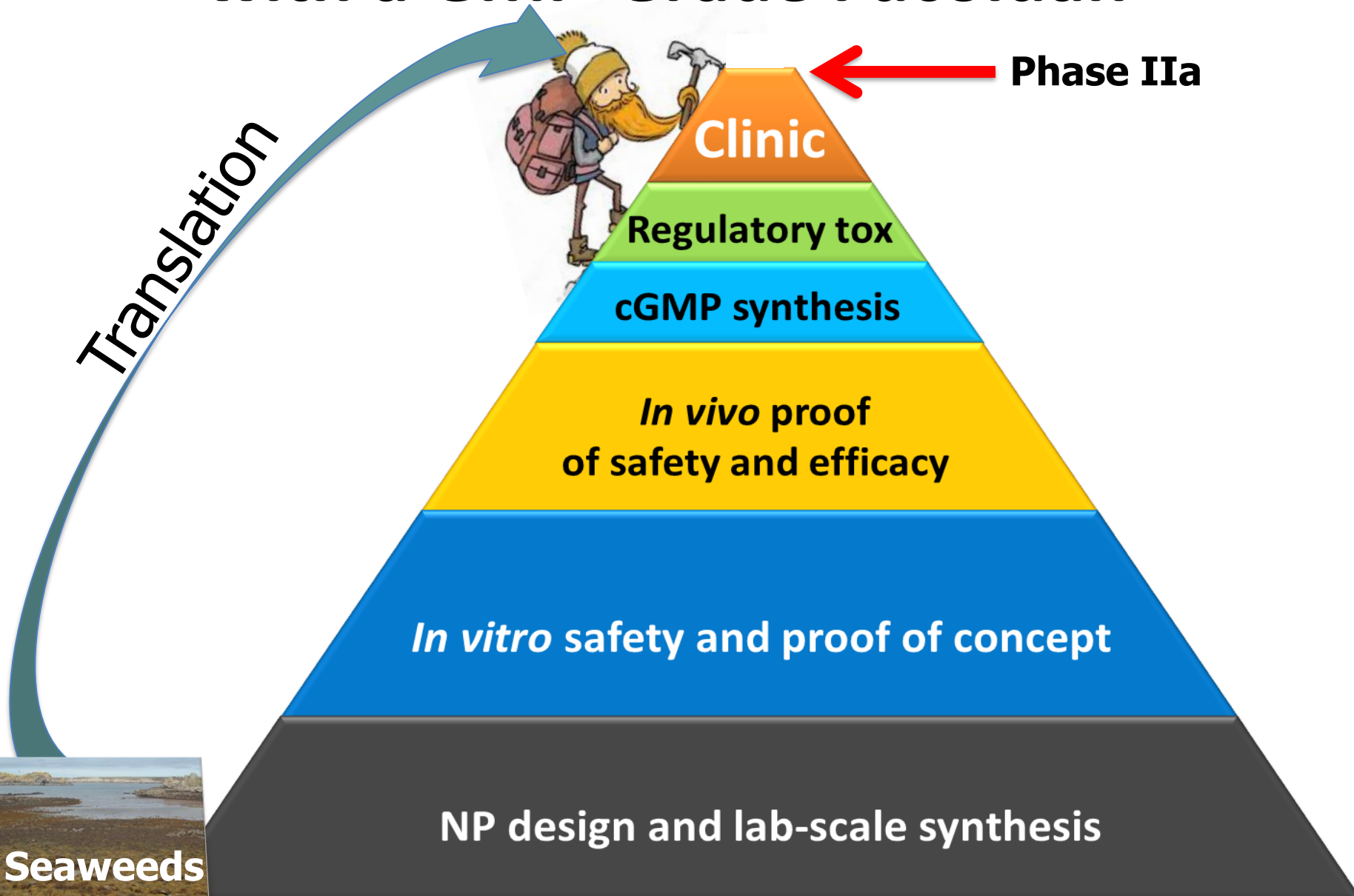
On going Phase II Clinical trial

Phase IIa clinical trial to evidence acute thrombogenic activity in patients with Deep Vein Thrombosis

Ongoing at AMC

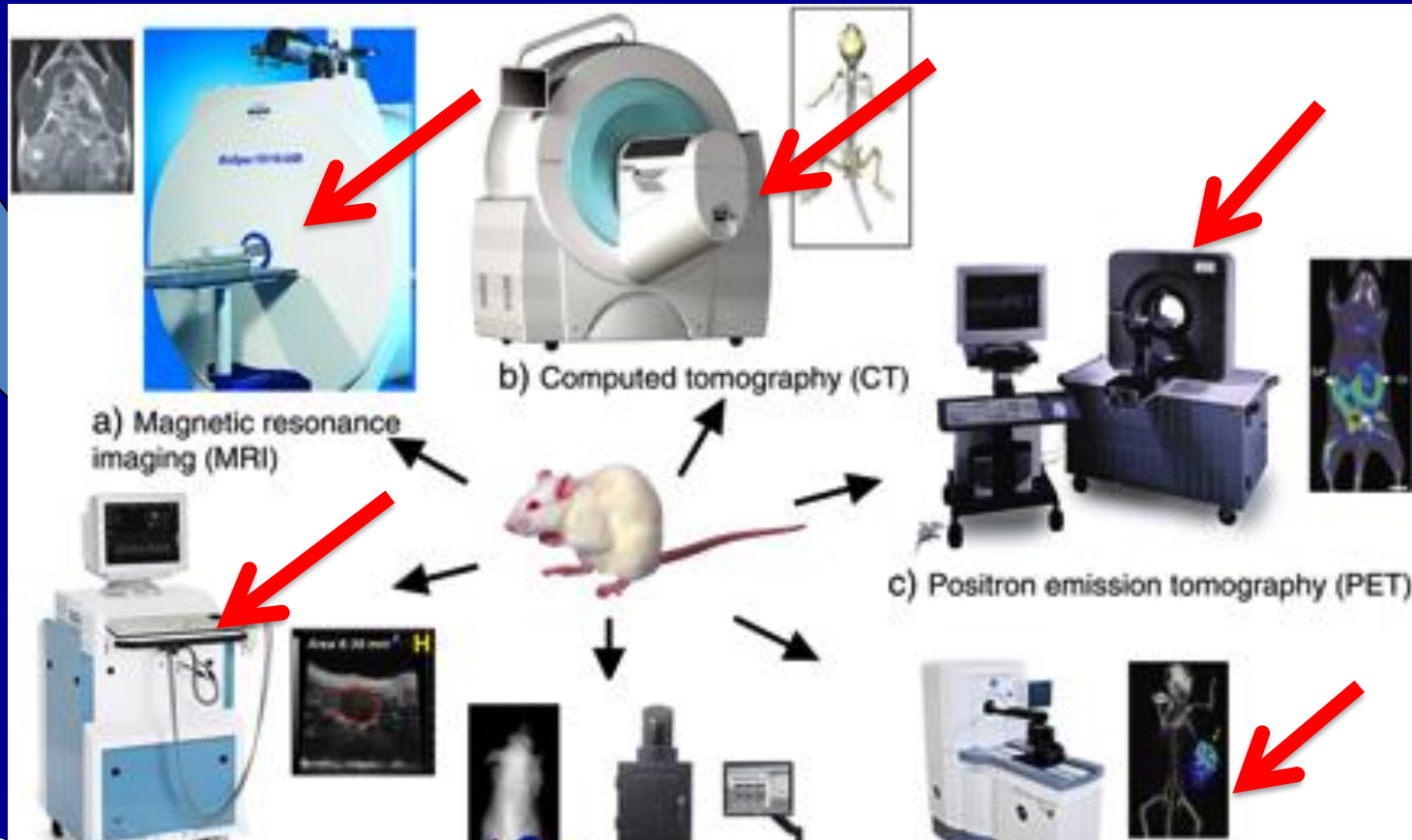


The Clinical Thrombus Imaging with a GMP-Grade Fucoïdan



Thrombus Imaging with Fucoïdan

NanoAthero



Theranostics
The Forum for Diagnostics, Imaging, and Therapy Research

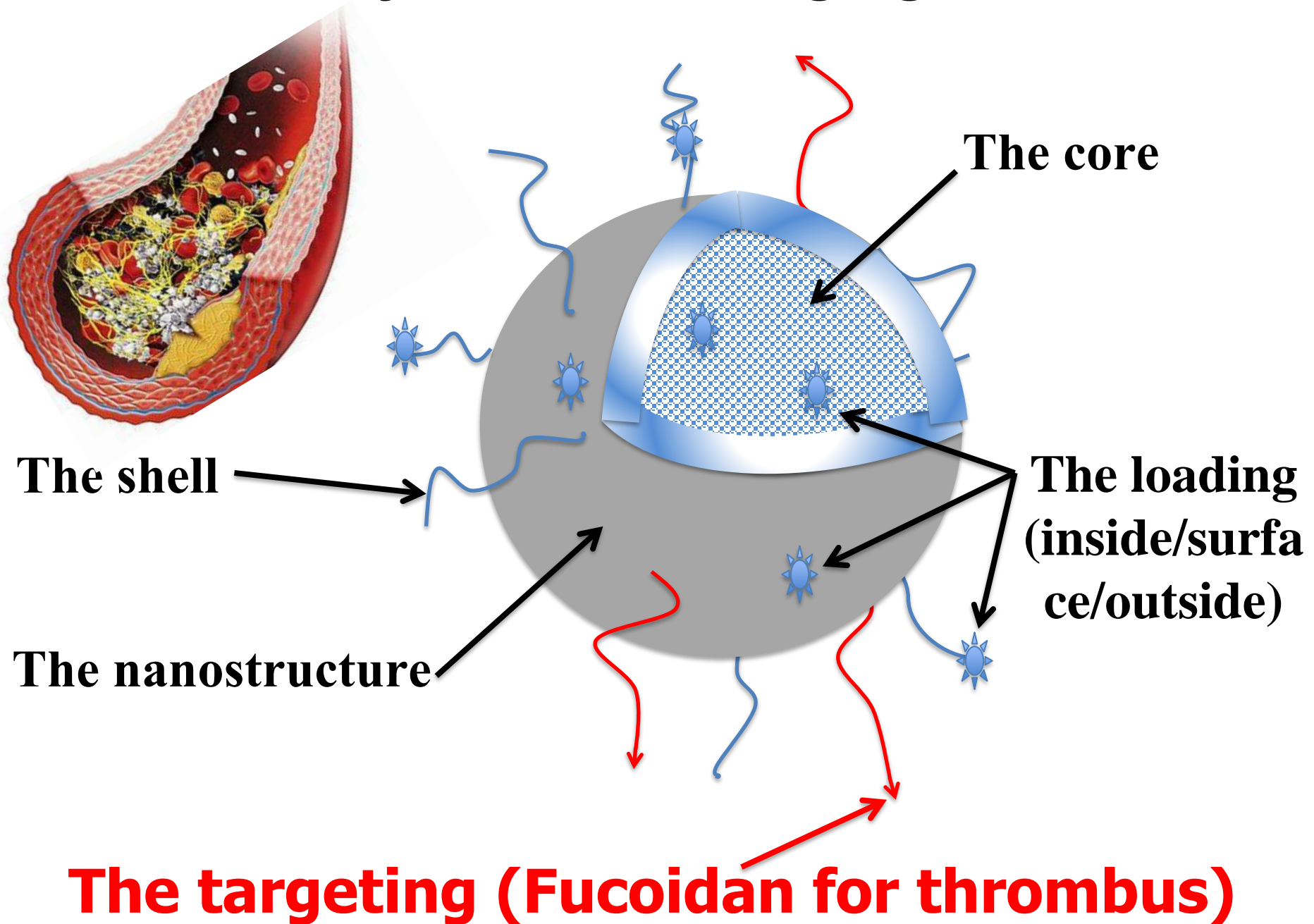
Polysaccharide Nanosystems
COVER FEATURE
Polysaccharide Nanosystems for Future Progress in Cardiovascular Pathologies
Silver A. K.A. et al.

IVYSPRING INTERNATIONAL PUBLISHER

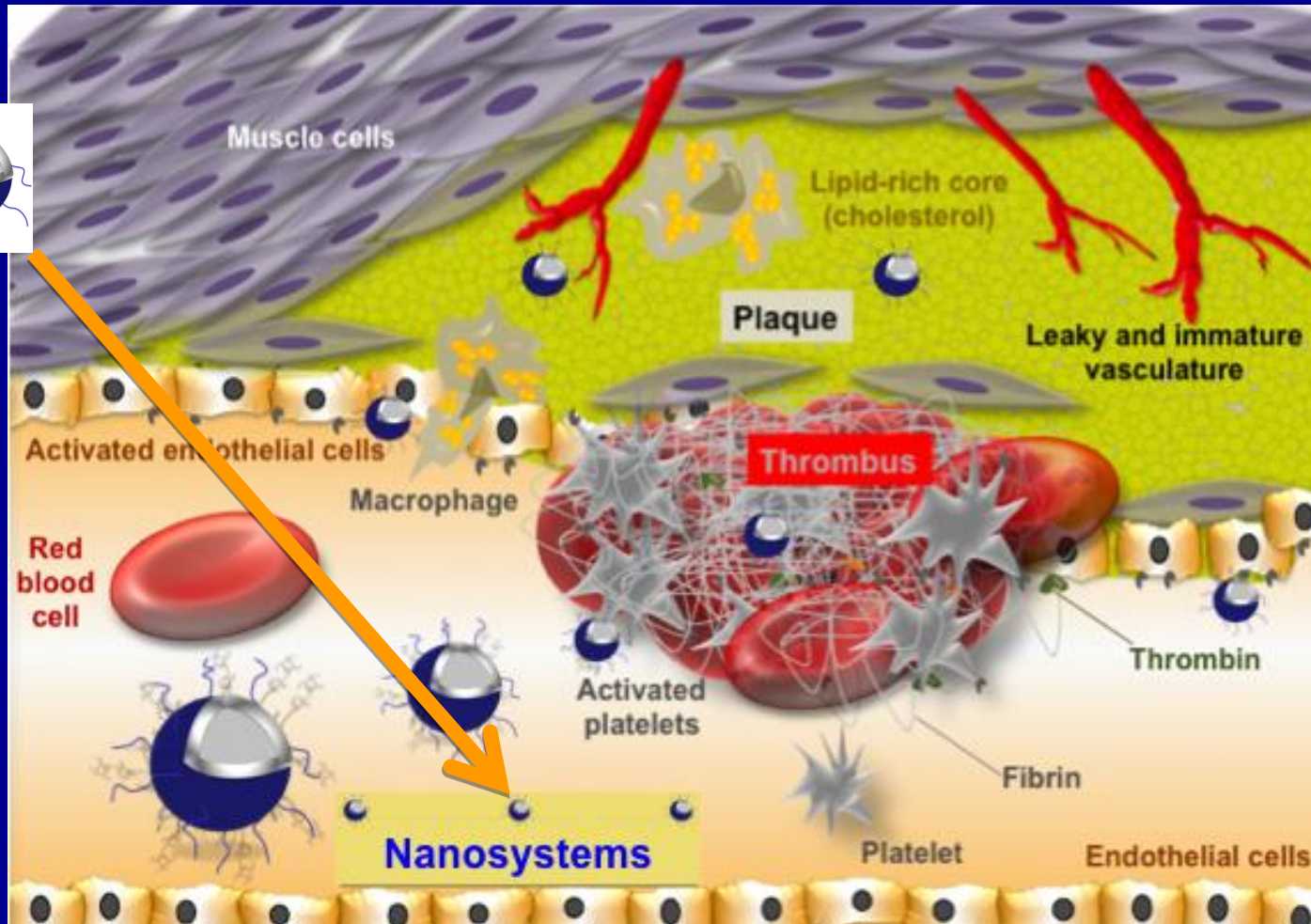
> 15 Publications
3 patents
Several Grants

**Preclinical Thrombus Imaging
... to Clinical Thrombus Imaging**

Nano/microsystems for imaging of thrombus



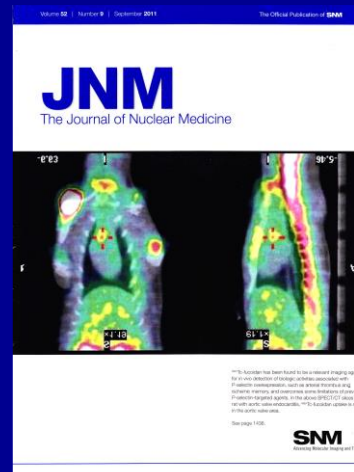
Targeted systems for Imaging of Thrombus



Large Scale NMP
FP7
2013-2019
D LETOURNEUR
Coordinator

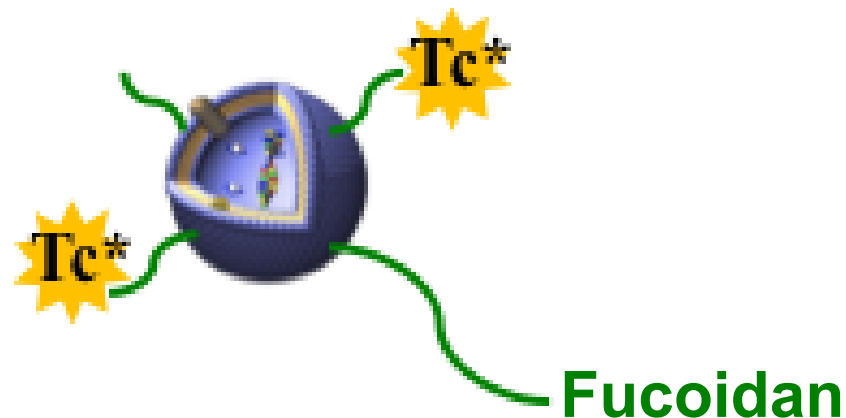
NanoAthero

AKA Silva et al, Theranostics + Cover June 2014
F. Rouzet et al, J Nucl Med + Cover Sept 2011



Fucoidan for *in vivo*

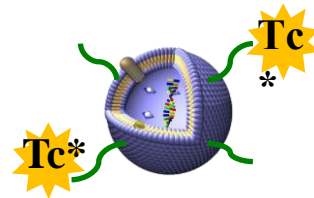
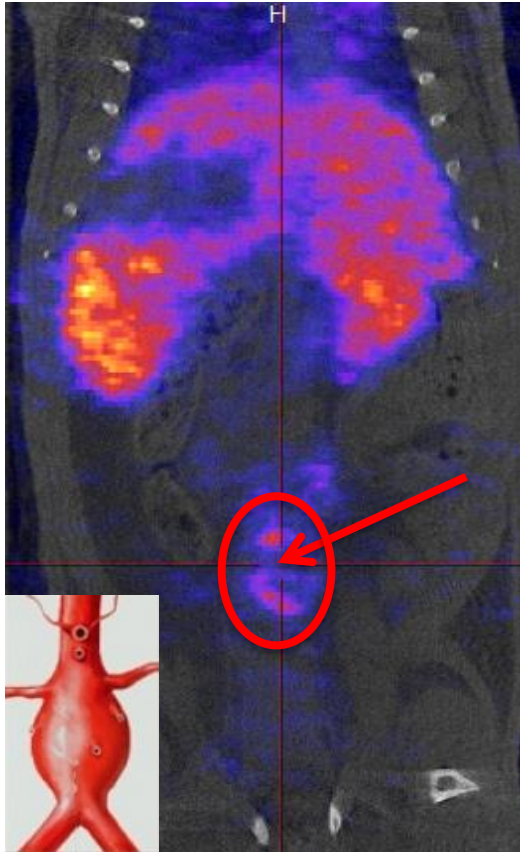
SPECT imaging of thrombus



Polysaccharide microparticles + ^{99m}Tc

Molecular Imaging of thrombus by SPECT

Microparticles + ^{99m}Tc
+ fucoidan



^{99m}Tc -MP-Fucoidan / AAA

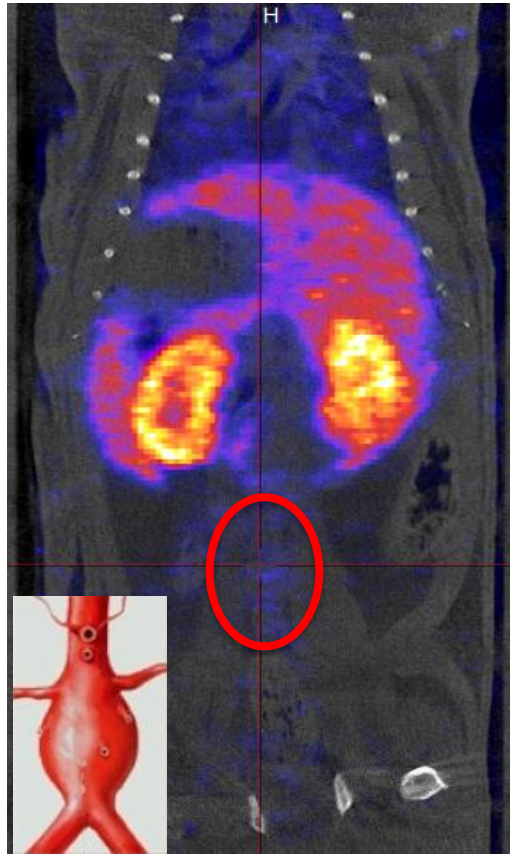
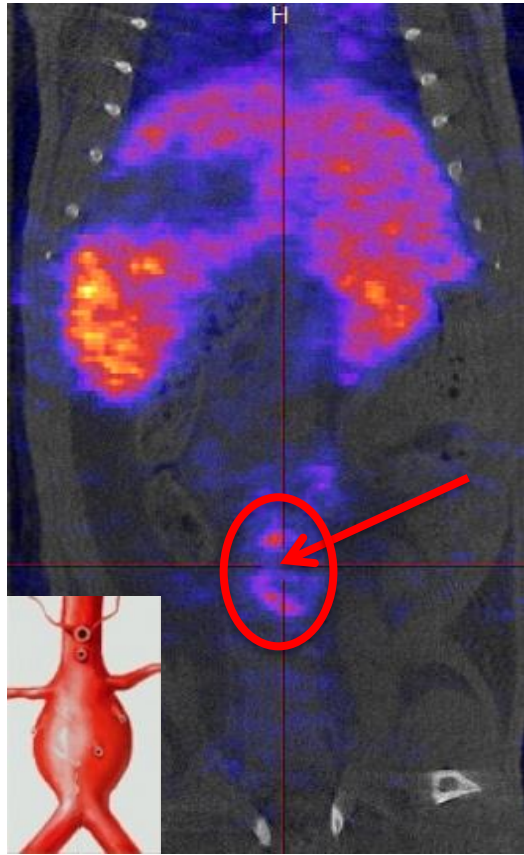
T. Bonnard *et al.*, ^{rat}Theranostics 2014

SPECT imaging at 2 hours

Molecular Imaging of thrombus by SPECT

Microparticles + ^{99m}Tc
+ fucoidan

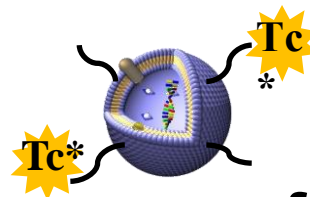
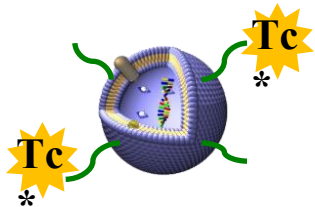
Microparticles + ^{99m}Tc
without fucoidan



SPECT imaging
at 2 hours

^{99m}Tc -MP-Fucoidan / AAA
rat

^{99m}Tc -MP / AAA rat



no fucoidan

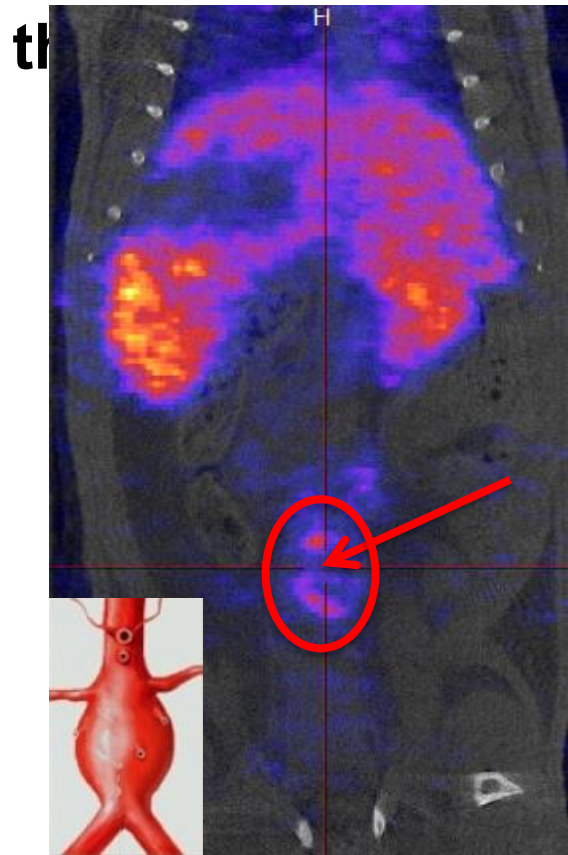
Molecular Imaging of thrombus by SPECT

Polysaccharide microparticles + ^{99m}Tc

+ fucoidan

without fucoidan

+ fucoidan (no



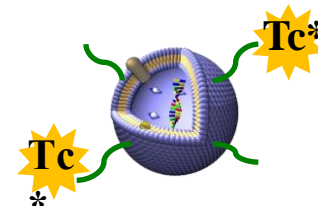
^{99m}Tc -MP-Fucoidan / AAA rat

^{99m}Tc -MP / AAA rat

^{99m}Tc -MP-Fucoidan / Healthy rat

SPECT imaging at 2 hours

T. Bonnard *et al.*, Theranostics 2014



Targeted systems for Imaging of Thrombus

NanoAthero

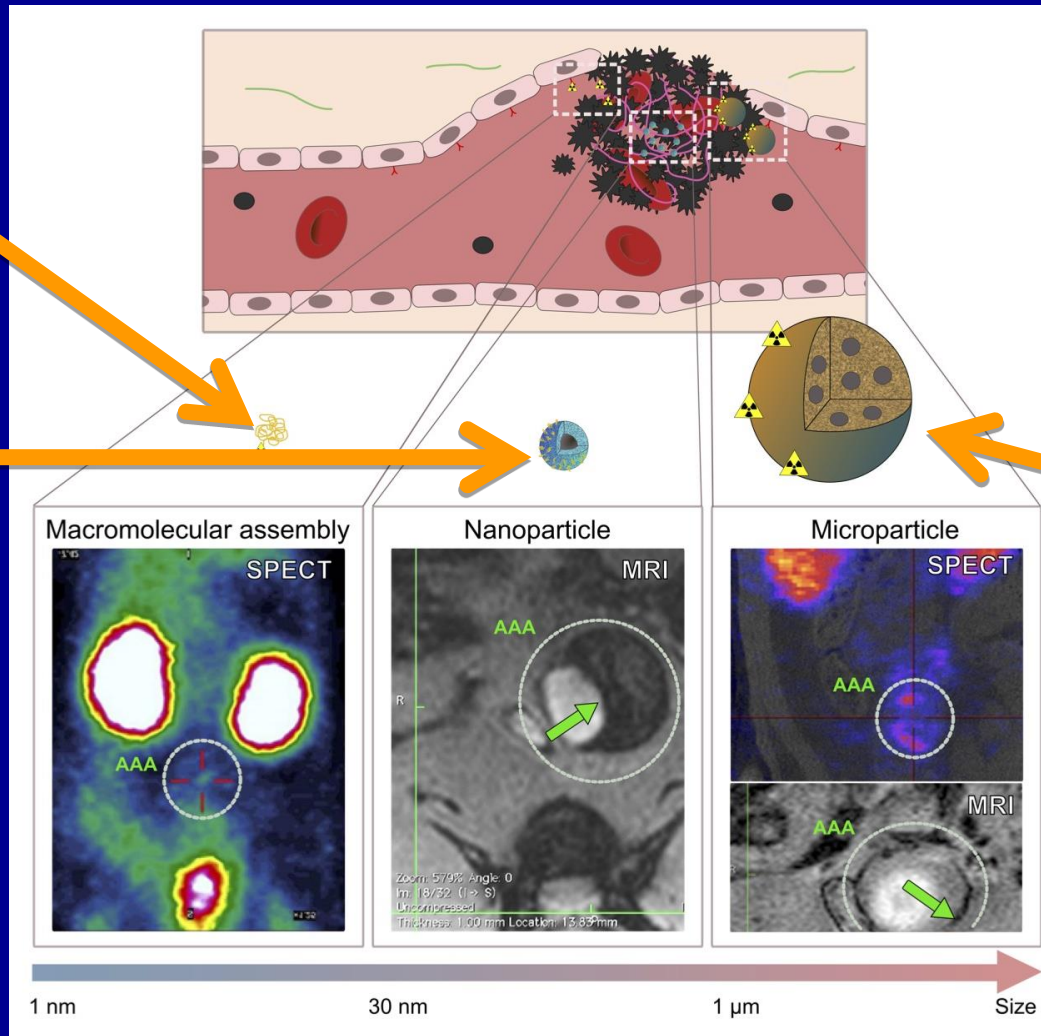
Polysaccharide

Composite Polysaccharide / iron oxyde

+ 2 other Patents

2015
2016

PATENT - PATENT - PATENT - PATENT



Large Scale
NMP FP7
2013-2019
D LETOURNEUR
Coordinator



Composite Polysaccharide beads

AKA. Silva et al, *Theranostics* + Cover June 2014

M. Suzuki et al., *Nanomedicine* 2015

M. Juenet et al., *Future Sci OA* 2015

J. Matuszak et al., *Nanomedicine* 2016

T. Bonnard et al., *Theranostics* 2014

T. Bonnard et al., *Acta Biomaterialia* 2014

M. Juenet et al., *BBRC* + Cover Dec 2015

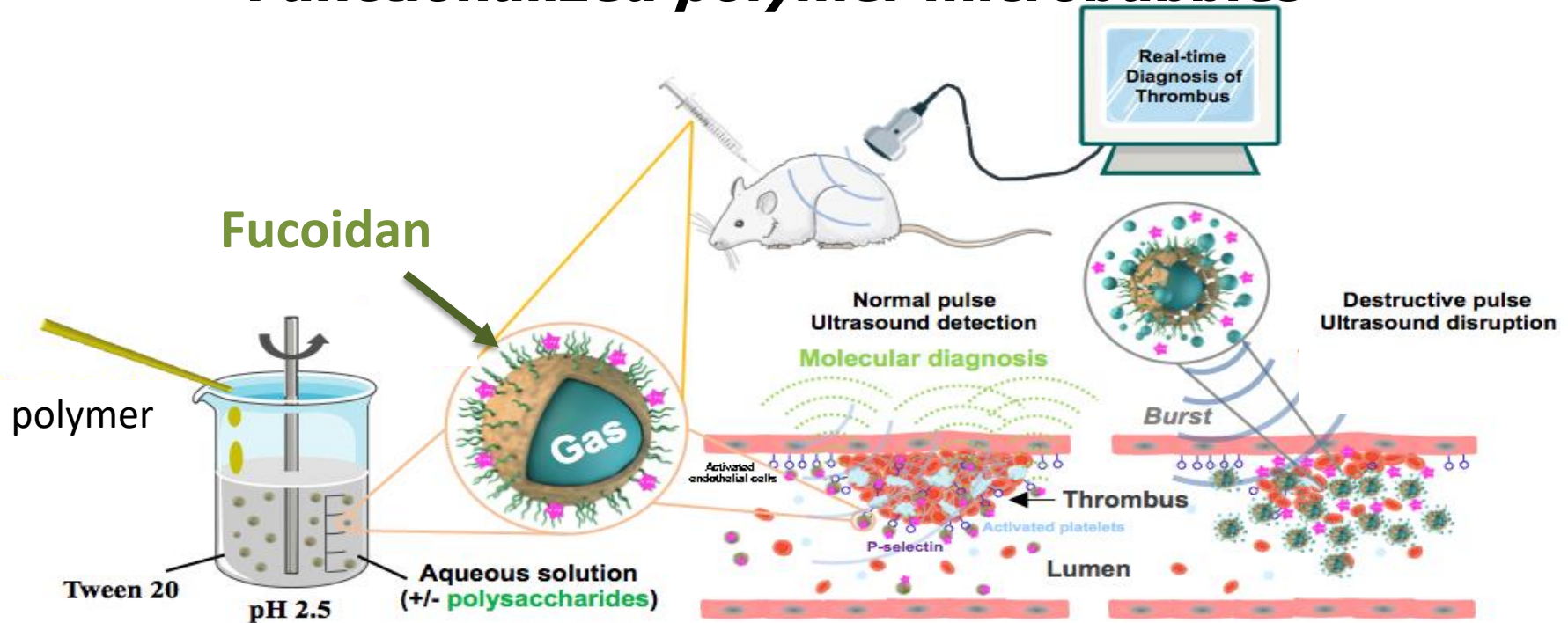
B. Li et al., *Adv Health Mater* + Cover 2017

Ultrasound developments



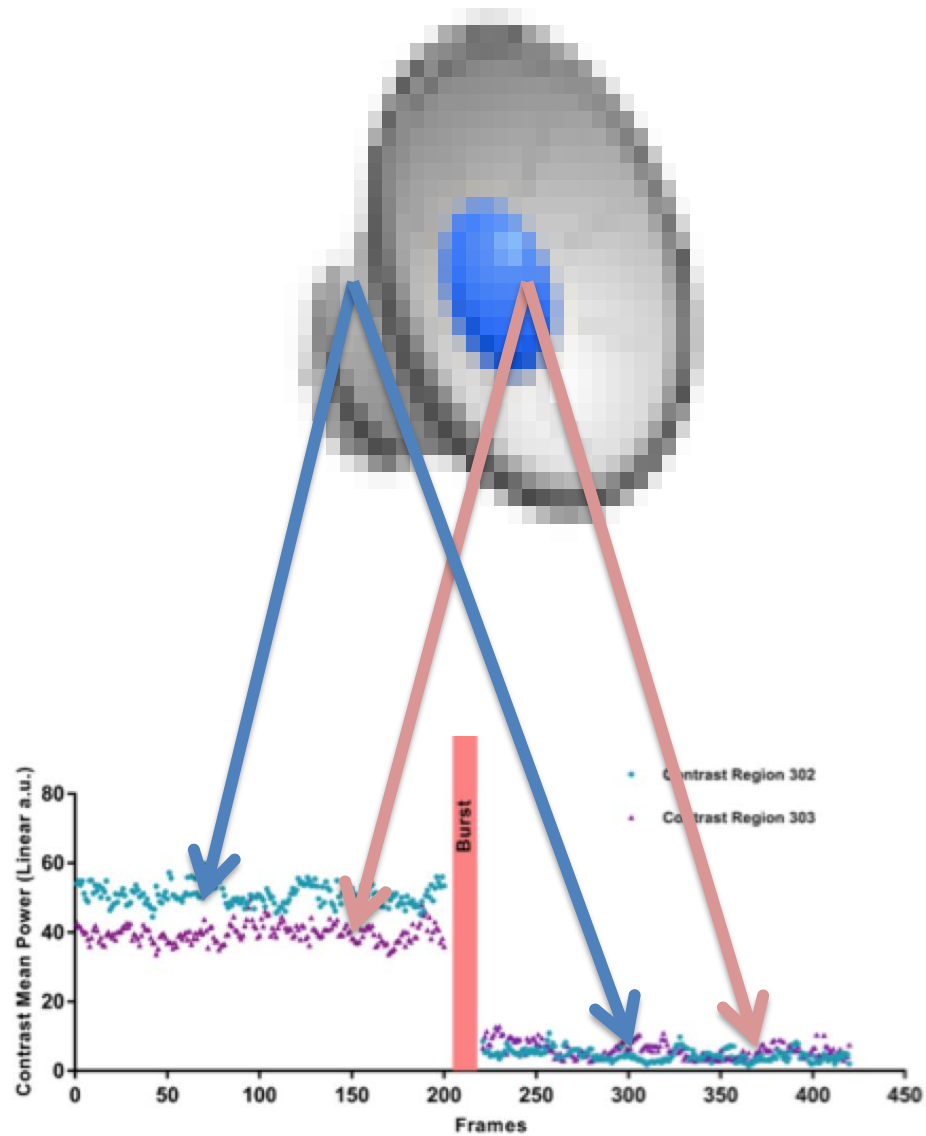
C Chauvierre

Functionalized polymer microbubbles

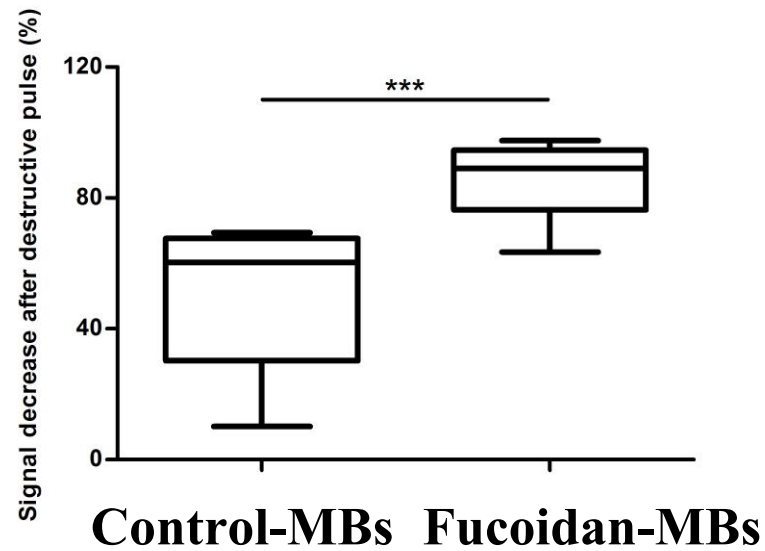
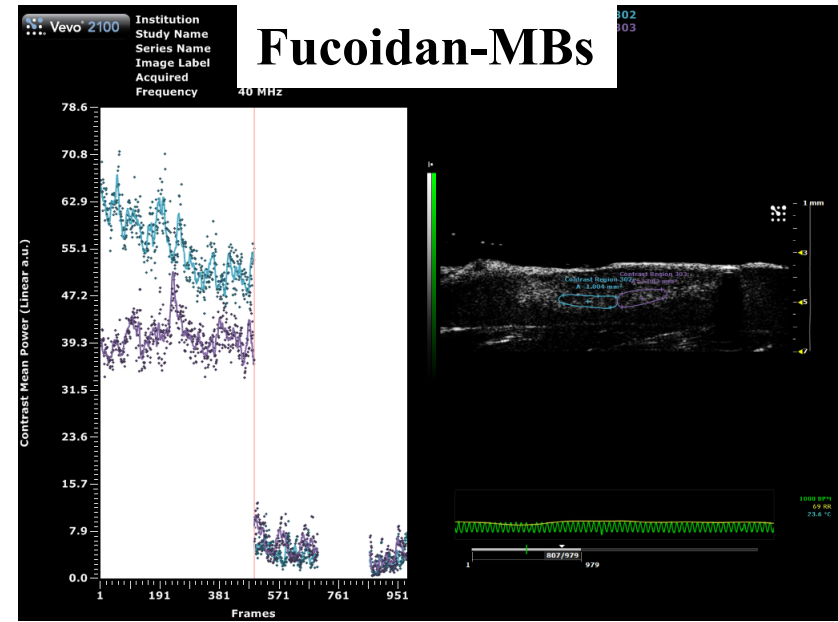
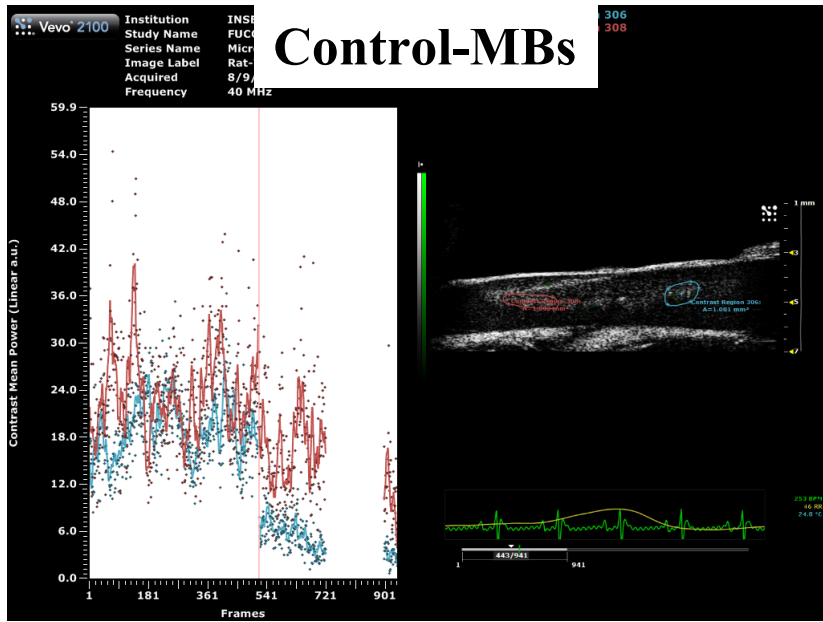


Bo, L. *et al.* Biomaterials 2019

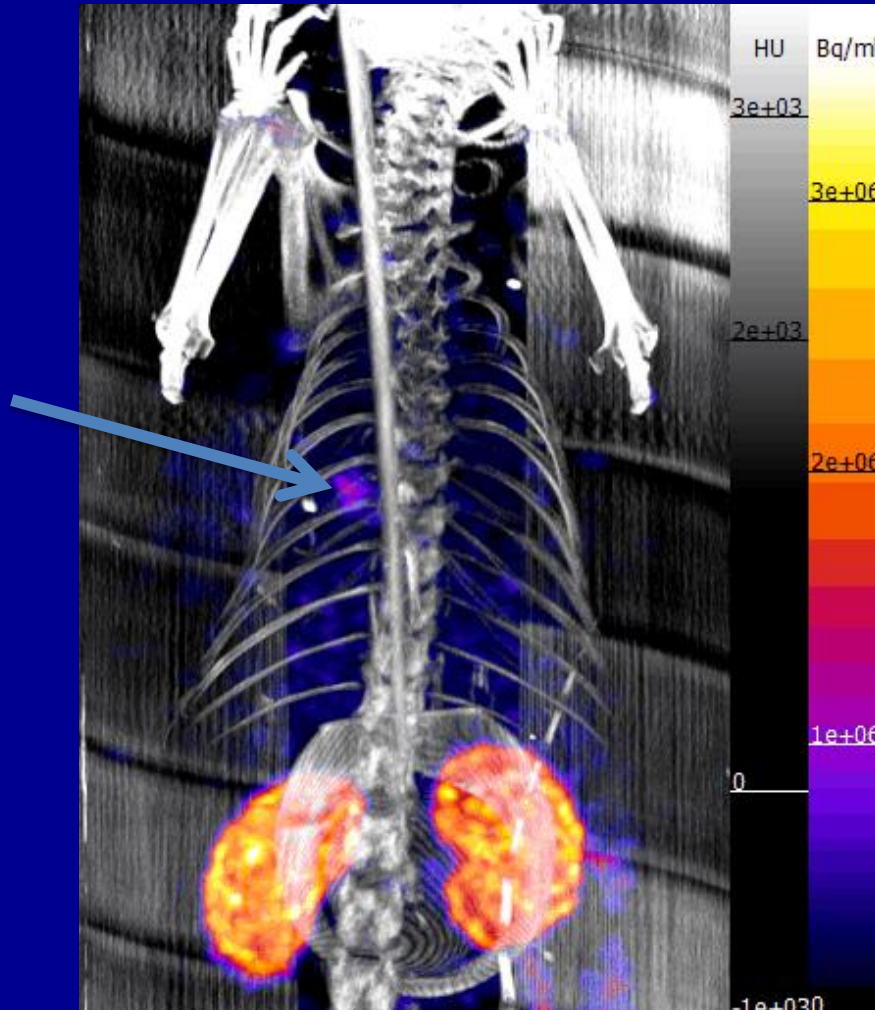
Injection of microbubbles



In vivo molecular imaging by US



Targeted systems for Imaging of Thrombus



F. Rouzet et al, J Nucl Med + **Cover** Sept 2011

AKA. Silva et al, Theranostics + **Cover** June 2014

M. Suzuki et al., Nanomedicine 2015

M. Juenet et al., Future Sci OA 2015

J. Matuszak et al., Nanomedicine 2016

T. Bonnard et al., Theranostics 2014

T. Bonnard et al., Acta Biomaterialia 2014

M. Juenet et al., BBRC+ **Cover** Dec 2015

B. Li et al., Adv Health Mater + **Cover** 2017

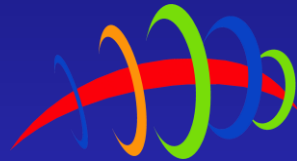
Lessons

Research on Molecular Imaging



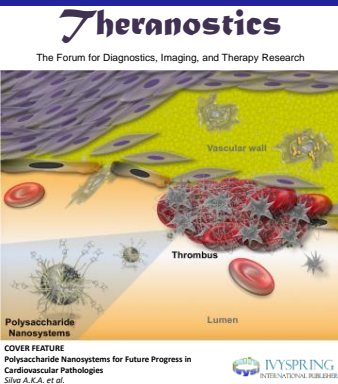
NanoAthero

LVTS
INSERM U1148



Clinic

+ several PhD & post-docs



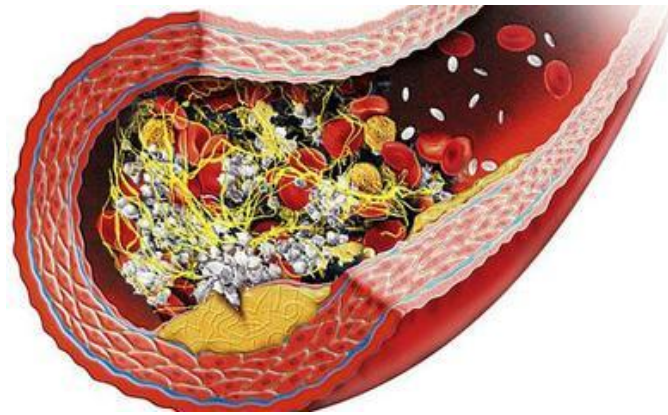
Research on Treatments

Juenet et al Biomaterials 2018; Li et al Biomaterials 2019

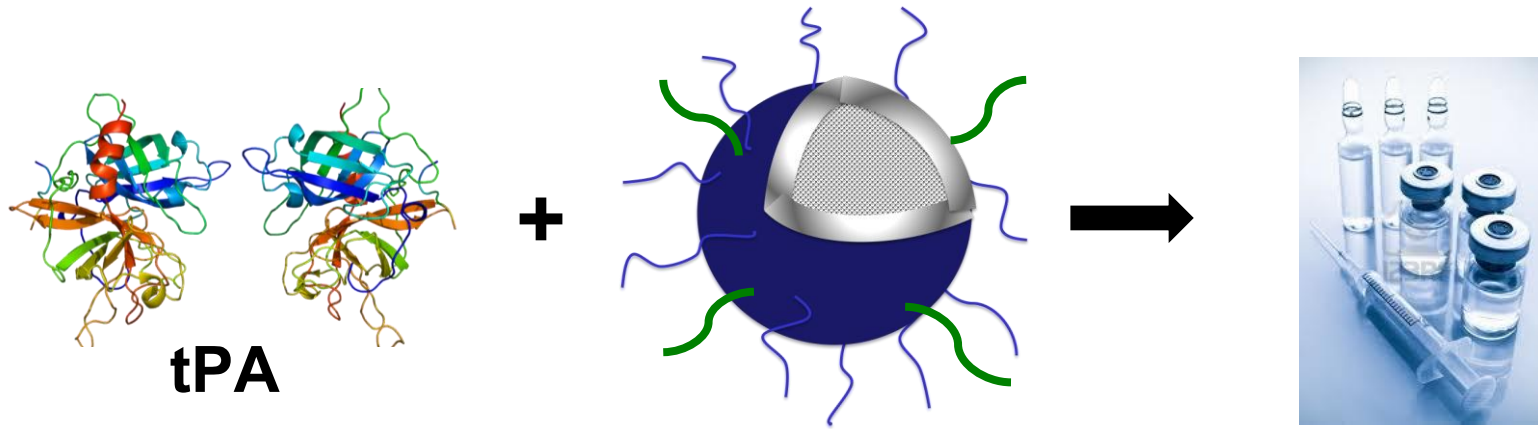
> 15
Publications
3 patents
Several Grants

and future industrial developments

Thrombus : treatment



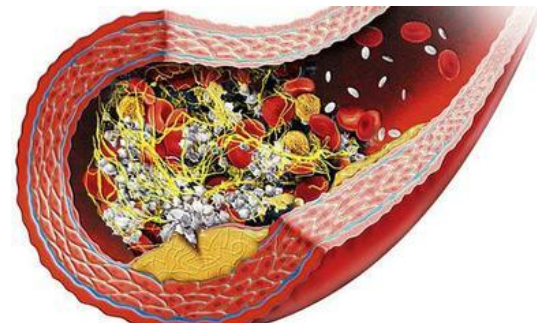
Therapeutic agent for thrombolysis



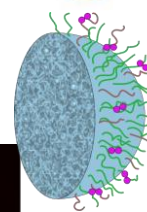
***The only fibrinolysis compound in human:
Tissue Plasminogen Activator (tPA)***

AIMS:

- ⇒ **Increase efficacy**
- ⇒ **Limited hemorrhage (controlled release and targeting)**
- ⇒ **Protection of degradation from PAI-1**



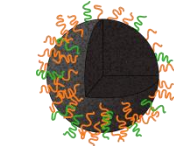
Targeted Polysaccharide Nanosystems for Thrombus Treatment



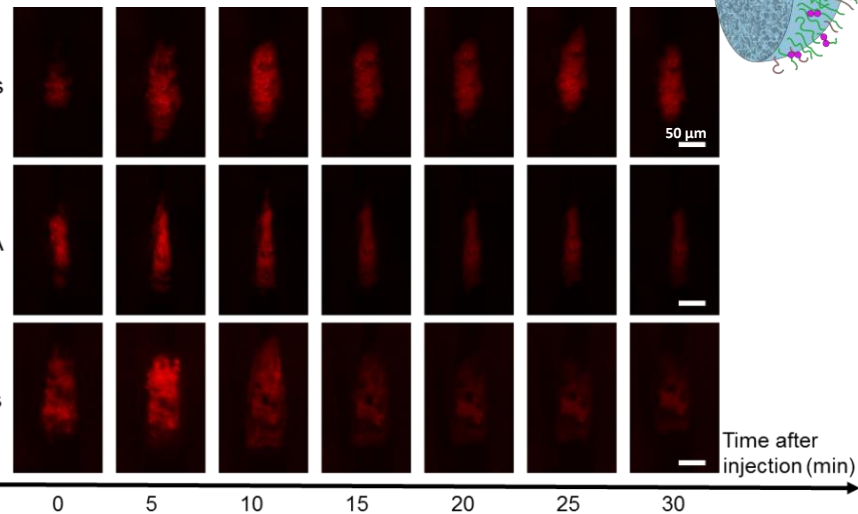
**Juenet *et al*,
Biomaterials 2018**



Thrombolysis

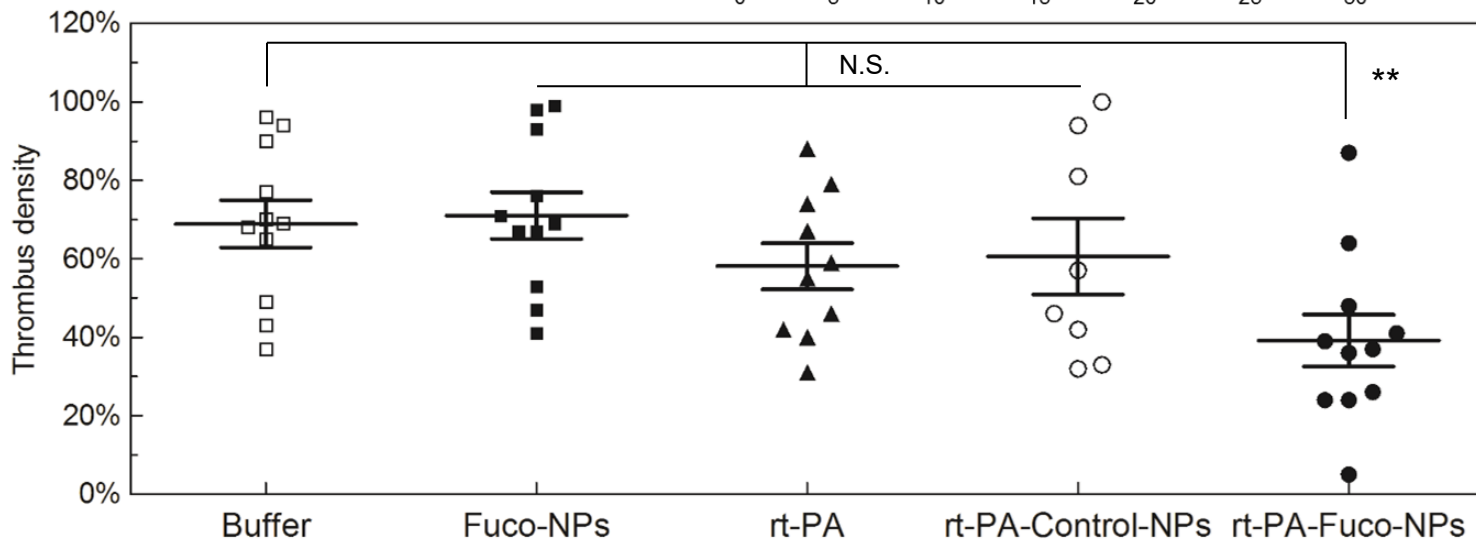


Fuco-NPs



Mouse mesenteric vein

Thrombus density at 30 minutes

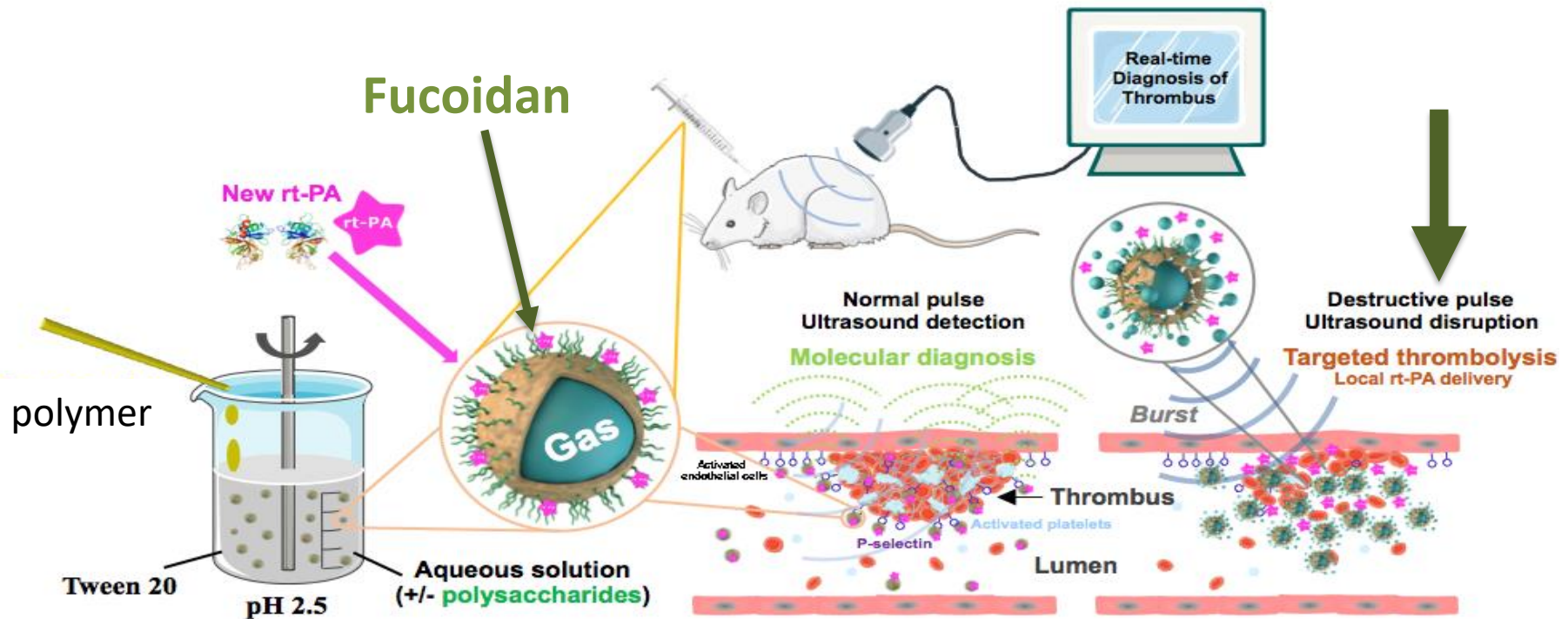


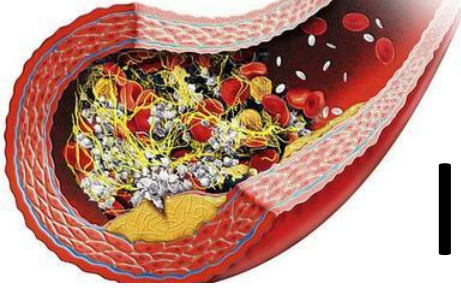
rt-PA dose (mg/kg)	-	-	2.4 ± 0.4	2.6 ± 0.3	2.4 ± 0.4
Thrombus density at 30 minutes	69% ± 6%	71% ± 6%	58% ± 6%	61% ± 10%	39% ± 7%

Ultrasound developments : C Chauvierre

Targeted therapy

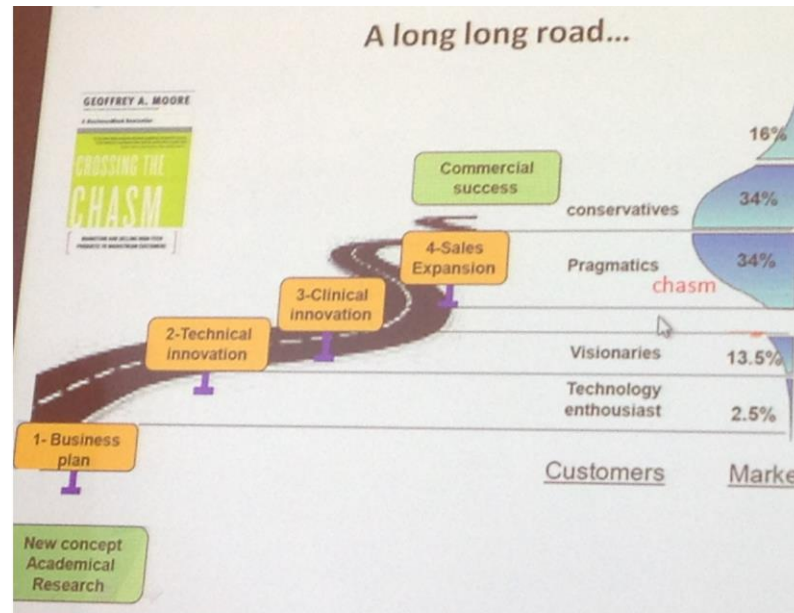
Functionalized polymer microbubbles





Thrombus : Imaging & Treatment

Fucoidan : From the design to the clinic (phase I, IIa)



A large expertise in Research and Industrial development

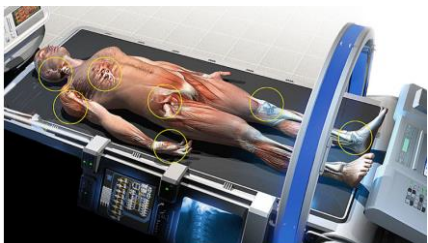
Research



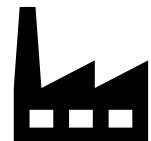
Laboratory for Vascular Translational Science



Atlantic Bio GMP va investir 2,7 millions d'euros dans la production de "cellules médicamenteuses" à Saint-Herblain (Loire-Atlantique)
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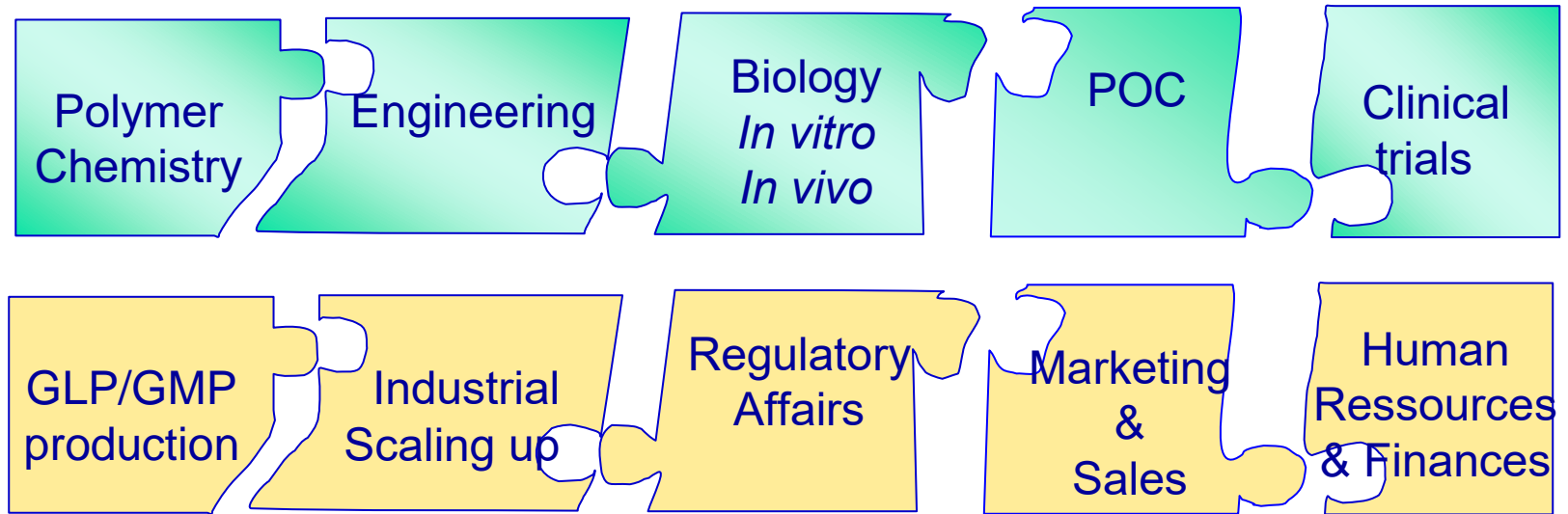


Industrial development



A need of large expertise

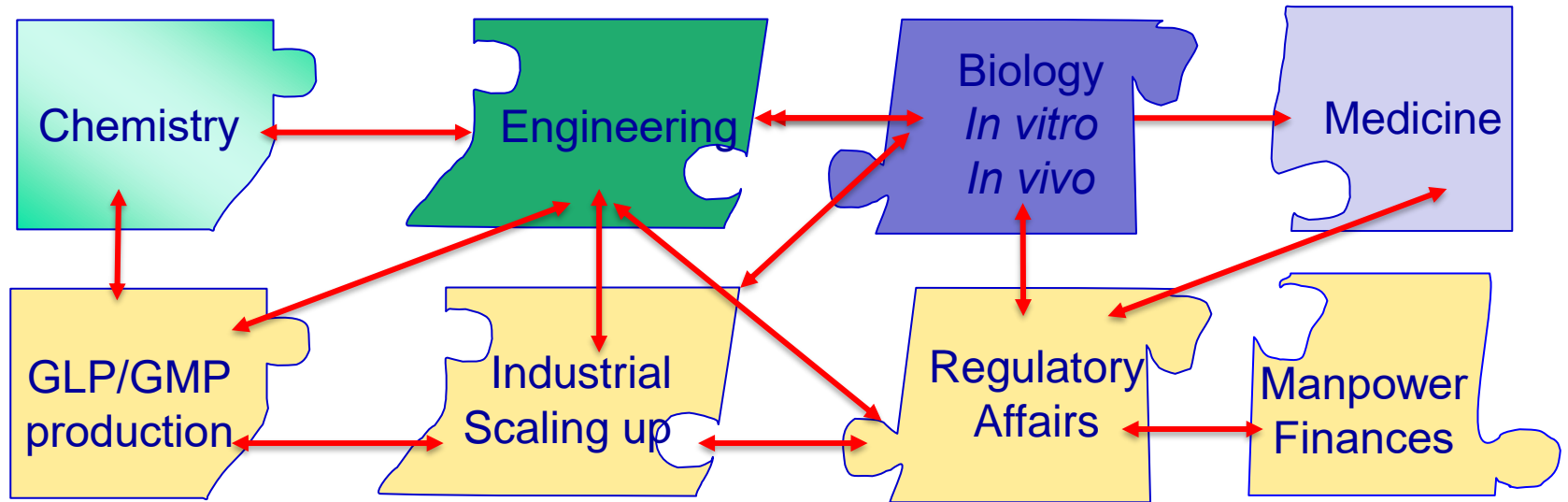
Research



Industrial development

A need of large expertise

Research



Industrial development

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Biomaterials

Volume 10, Issue 6, August 1989, Pages 363-368

1989



New natural polysaccharides with potent antithrombic activity: fucans from brown algae

V. Grauffel *, B. Kloareg **, S. Mabeau **, P. Durand †, J. Jozefonvicz * 

* Laboratoire de Recherches sur les Macromolécules, CNRS UA 502, Université Paris-Nord, Av. J.B. Clément, 93430 Villetaneuse, France

** Centre d'Etudes Océanologiques et de Biologie Marine, CNRS LP 4601, Place G. Tessiers, 29211 Roscoff, France

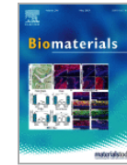
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CEVA

Centre d'Études et de Valorisation des Algues



Le CEVA, est le centre technique des Algues. Créé en 1982, il réalise des prestations d'études sous contrat,

des expertises techniques et assiste les entreprises dans leurs développements de produits et procédés intégrant des algues. Il est labellisé ITAI par le ministère de l'Agriculture et des Pêches.

Son savoir-faire couvre à la fois les domaines de l'environnement, de la culture, de la chimie des constituants algaux et des procédés de traitement appliqués aux algues.

CEVA (Algae Technology Center) was created in 1982 to promote algae applications within various markets (agriculture, food, feed, chemistry, material). It performs studies under contract, technical expertise and helps companies in their development of new products or processes integrating algae. CEVA is certified ITAI by the French Ministry of Agriculture and Fisheries. CEVA's know-how covers ecology, culture of algae, chemistry of algal components



 **2 M€ de CA**
25 personnes
550 contacts/an avec des entreprises



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Volume 10, Issu

New natural polysacc antithrombic activity

V. Grauffel *, B. Kloareg **, S. Mabeau



VEGENOV – BBV

Vegenov, aux côtés du CTIFL et en complémentarité avec cet institut national, propose des services de conseil et recherche appliquée aux entreprises du végétal. Les compétences clés de Végenov (biologie cellulaire et moléculaire, microbiologie et expérimentations agronomiques et analyses sensorielles et nutritionnelles) appliquées à tout type d'espèce permettent de répondre à trois objectifs de recherche et développement :

- appuyer les entreprises dans leurs programmes de création variétale,
- optimiser les systèmes de protection et nutrition des plantes,
- et améliorer la qualité des produits végétaux

Contact Direction : Serge Mabeau. mabeau@vegenov.com



Directeur de BBV, Serge Mabeau prépare activement la journée d'accueil du grand public dans ses labos.

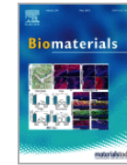
Forte d'une vingtaine de chercheurs et techniciens au service des filières végétales, Bretagne Biotechnologie Végétale (BBV) que dirige Serge Mabeau est l'outil biotechnologique dont se sont dotés les agriculteurs de la filière légumière régionale « Prince de Bretagne » depuis 1989.

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MENU 

Catherine Boyen, directrice de la Station biologique

Ouest-France
Publié le 28/01/2019 à 01h40

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ÉCOUTER

LIRE PLUS TARD

PARTAGER



Passation de pouvoir à la SBR entre Bernard et Catherine. | OUEST-FRANCE



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Station Biologique
de Roscoff

Le fait a été officialisé le 1^{er} janvier. Le directeur de la Station biologique de Roscoff (SBR), Bernez Kloareg (Bernard Cloarec à l'état civil) a fait valoir ses droits à la retraite. Catherine Boyen, directrice de recherche en biologie marine à la station, lui succède. Pour autant, le néoretraité n'arrête pas là ses fonctions puisqu'il conserve l'envie de suivre le projet Blue Valley, qu'il a initié et développé.

L'édition numérique du
samedi 6 mai 2023

Le Télégramme

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« La science n'a ni religion, ni politique » : une maxime, inscrite sur la porte de l'aquarium originel de la Station, à laquelle Catherine Boyen pourrait y ajouter « ni genre », tant elle entend pousser les femmes au sommet de la recherche. (Photo S.G.)

À la tête de la Station biologique de Roscoff (29) depuis 2019, Catherine Boyen est la première femme à occuper ce poste en 150 ans d'histoire. Forte d'un solide parcours scientifique, elle met son énergie et ses valeurs féministes au service de la recherche.

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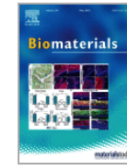
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2019



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LA STATION 150 ANS DE LA SBR RECHERCHE ENSEIGNEMENT OBSERVATION SERVICES ACTUALITÉ ARCHIVES HAL



CATHERINE BOYEN

Directeur de recherche CNRS

DIRECTRICE DE LA STATION BIOLOGIQUE DE ROSCOFF



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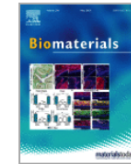


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**Véronique
(Grauffel)
Letourneur**

**Charly
Letourneur**

**Didier
Letourneur**

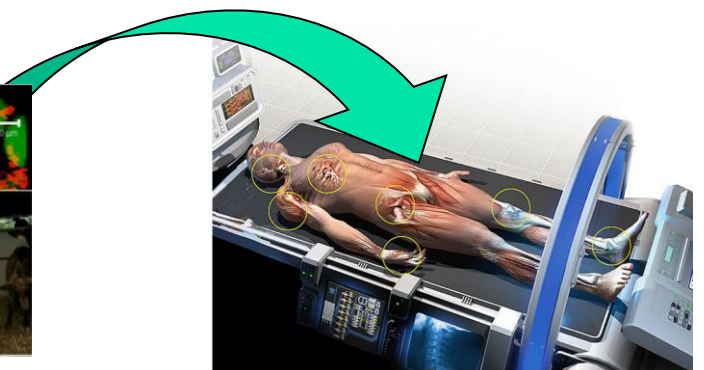
CONCLUSIONS

Not a linear development scheme

*Need time, expertise, money,
a lot of work*

... and people

Acknowledgements





CONGRÈS FRANÇAIS
d'HÉMOSTASE

10-12
MAI
2023

PROGRAMME



Didier Letourneur

didier.letourneur@inserm.fr