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Biological evaluations of nanocarriers to improve the effectiveness of colorectal cancer treatment

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LIST OF ABBREVIATIONS

ACE	Acetone
ACE	Apoptosis-inducing factor
AFM	Atomic force microscopy
AP	Aqueous Phase
APAF-1	Anti-apoptotic protease activating factor 1
ASGP	Asialoglycoprotein
ATR-FTIR	Transform infrared spectroscopy
AuNPs	Gold NPs
BBB	Blood-brain barrier
BTB	Blood-tumor barrier
BSA	Bovine serum albumin
CAP	Capecitabine
CCL22	Chemokine ligand 22 of the C-C motif
CHOL/CHO	Cholesterol
CRC	Colorectal cancer
CT	Threshold cycle
CVDL	Carvedilol
CXCR4	C-X-C chemokine receptor type 4
DAPI	Diamidino-2-phenylindole; 4,6-diamidino-2-phenylindole
DCM	Dichloromethane
DDS	Drug delivery systems
DISC	Death-inducing signaling complex
DMEM	Dulbecco's modified eagle medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
DSL	Dynamic light scattered
EDTA	Ethylenediamine tetraacetic acid
EE	Encapsulation efficiency
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMT	Epithelial-mesenchymal transition
EPR	Enhanced Permeation and Retention
FA	Folic Acid
FAAD	Fas-associated death domain protein
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FITC	Fluorescein isothiocyanate
GSH	Glutathione

HA	Hyaluronic acid
HRP	Haptoglobin Related Protein
IAP	Apoptosis inhibitor proteins
IHC	Immunohistochemistry
IRI	Irinotecan
LAS X	Leica Application Suite X
MDA	Malondialdehyde
MDR-1	Multidrug resistance protein 1
MOMP	Mitochondrial outer membrane permeabilization
MPS	Mononuclear phagocyte system
mRNA	Messenger ribonucleic acids
MSNs	Mesoporous silica NPs
MTS	[3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt]
mV	Millivolt
NADPH	Nicotinamide adenine dinucleotide phosphate?
NF-kb	Factor nuclear kappa B
NHS	N-hydroxysuccinimide
NIR	Near infrared 780 dye
Nm	Nanometer
NPs	Nanoparticles
OXA	Oxaliplatin
PAA	Polyacrylic acid
PBS	Phosphate-buffered saline
PCL	Poly- ϵ -caprolactone
PDI	Polydispersity Index
PEG	Polymeric polyethylene glycol
PLA	Polymers polylactic acid
PLGA	Poly (D, L-lactide-co-glycolide)
PTX	Paclitaxel
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
qPCR	Real-time quantitative polymerase chain reaction
RA	Retinoic acid
RAR	Retinoic acid receptor
RES	Reticuloendothelial system
RNA	Ribonucleic acid
RNI	Reactive nitrogen intermediates
ROS	Reactive oxygen species

RP-HPLC	Reversed-phase high-performance liquid chromatography
RT-PCR	Reverse transcription polymerase chain reaction
RXR	Retinoid X receptor
SMAC	Second mitochondria-derived activator of caspases
SD	Standard deviation
STAT-3	Signal transducers and activators of transcription
TCA	Trichloroacetic acid
TEA	Triethylamine
TEM	Transmission electron microscopy
TGF- β	Transforming growth factor beta
TMA	Tissue microarray
TME	Tumor microenvironment
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

LIST OF PUBLICATIONS

1. Nanocarriers as a Tool for the Treatment of Colorectal Cancer. Ana Luiza C. de S. L. Oliveira, Timo Schomann, Lioe-Fee de Geus-Oei, Ellen Kapiteijn, Luis J. Cruz*, Raimundo F. de Araújo Júnior*. August 2021. *Pharmaceutics*. DOI: 10.3390/pharmaceutics13081321. * Authors to whom correspondence should be addressed.
2. Maximizing the potency of oxaliplatin coated nanoparticles with folic acid for modulating tumor progression in colorectal cancer. Ana Luiza C. de S. L. Oliveira, Luana Zerillo, Luis J. Cruz*, Timo Schomann, Alan B. Chan, Thaís Gomes de Carvalho, Shirley Vitória de P. Souza, Aurigena A. Araújo, Lioe-Fee de Geus-Oei, Raimundo F. de Araújo Júnior*. January 2021. *Materials Science and Engineering C*. DOI: 10.1016/j.msec.2020.111678. * Authors to whom correspondence should be addressed.
3. Cholesterol-functionalized carvedilol-loaded PLGA nanoparticles: anti-inflammatory, antioxidant, and antitumor effects. Ana Luiza C. de S. L. Oliveira, Alaine M. dos Santos-Silva, Arnóbio A. da Silva-Júnior, Vinícius B. Garcia, Aurigena A. de Araújo, Lioe-Fee de Geus-Oei, Alan B. Chan, Luis J. Cruz and Raimundo F. de Araújo Júnior. May 2020. *Journal of Nanoparticle Research*. DOI: 10.1007/s11051-020-04832-8
4. Effect of Oxaliplatin-Loaded Poly (d,l-Lactide-co-Glycolic Acid) (PLGA) Nanoparticles Combined with Retinoic Acid and Cholesterol on Apoptosis, Drug Resistance, and Metastasis Factors of Colorectal Cancer. Ana Luiza C. de S. L. Oliveira, Raimundo Fernandes de Araújo Júnior*, Thaís Gomes de Carvalho, Alan B. Chan, Timo Schomann, Filippo Tamburini, Lioe-Fee de Geus-Oei and Luis J. Cruz*. February 2020. *Pharmaceutics*. DOI: 10.3390/pharmaceutics12020193. * Authors to whom correspondence should be addressed.
5. Self-Assembled Benzimidazole-Loaded Cationic Nanoparticles Containing Cholesterol/Sialic Acid: Physicochemical Properties, *In Vitro* Drug Release and *In Vitro* Anticancer Efficacy. Alaine Maria dos Santos-Silva, Lília Basílio de Caland, Ednaldo Gomes do Nascimento, Ana Luiza C. de S.L. Oliveira, Raimundo F. de Araújo-Júnior, Alianda Maira Cornélio, Matheus F. Fernandes-Pedrosa and Arnóbio Antônio da Silva-Júnior.

May 2019. International Journal of Molecular Sciences 20(9). DOI: 10.3390/ijms20092350

6. Hydrophilic and hydrophobic polymeric benzimidazole-loaded nanoparticles: Physicochemical properties and *in vitro* antitumor efficacy. Alaine Maria dos Santos Silva, Lilia Basílio de Caland, Polyanne Nunes de Melo Doro, Ana Luiza C. de S. L. Oliveira, Raimundo F. de Araújo-Júnior, Matheus F. Fernandes-Pedrosa, Eryvaldo Sócrates Tabosa do Egito, Arnóbio Antônio da Silva-Junior. April 2019. Journal of Drug Delivery Science and Technology. DOI: 10.1016/j.jddst.2019.04.005.

7. Designing structural features of novel benzimidazole-loaded cationic nanoparticles for inducing slow drug release and improvement of biological efficacy. Alaine M. dos Santos-Silva, Lilia B. de Caland, Ana Luiza C. de S. L. Oliveira, Raimundo F. de Araújo-Júnior, Matheus F. Fernandes-Pedrosa, Alianda Maira Cornélio, Arnóbio A. da Silva-Júnior. April 2017. Materials Science and Engineering C. DOI: 10.1016/j.msec.2017.04.053

8. Anti-inflammatory, analgesic and anti-tumor properties of gold nanoparticles. Raimundo Fernandes de Araújo Júnior, Aurigena Antunes de Araújo, Jonas Bispo Pessoa, Francisco Paulo Freire Neto, Gisele Ribeiro da Silva, Ana Luiza C.S. Leitão Oliveira, Thaís Gomes de Carvalho, Heloiza F.O. Silva, Mateus Eugênio, Celso Sant'Anna, Luiz H.S. Gasparotto. September 2016. Pharmacological reports. DOI: 10.1016/j.pharep.2016.09.017

9. Environmentally compatible bioconjugated gold nanoparticles as efficient contrast agents for colorectal cancer cell imaging. Kássio M.G. Lima, Raimundo F. Araújo Júnior, Aurigena A. Araújo, Ana Luiza C.S. Leitão Oliveira and Luiz H.S. Gasparotto. February 2014. Sensors and Actuators B Chemical. DOI: 10.1016/j.snb.2014.02.008.

10. The use of EEM fluorescence data and OPLS/UPLS-DA algorithm to discriminate between normal and cancer cell lines: A feasibility study. Ana Carolina de Oliveira Neves, Raimundo Fernandes de Araújo Júnior, Ana Luiza Cabral de Sá Leitão Oliveira, Aurigena Antunes de Araújo and Kássio Michell Gomes de Lima. April 2014. The Analyst. DOI: 10.1039/c4an00296b

11. Telmisartan induces apoptosis and regulates Bcl-2 in human renal

cancer cells. Raimundo Fernandes de Araújo Júnior*, Ana Luiza C.S. Leitão Oliveira*, Raniere Fagundes de Melo Silveira, Hugo Alexandre de Oliveira Rocha, Pedro de França Cavalcanti, and Aurigena Antunes de Araújo.

*These authors contributed equally. August 2014. *Experimental Biology and Medicine*. DOI: 10.1177/1535370214546267. * Equal contribution.

12. Maytenus ilicifolia dry extract protects normal cells, induces apoptosis and regulates Bcl-2 in human cancer cells. Raimundo Fernandes de Araújo Júnior*, Ana Luiza Cabral de Sá Leitão Oliveira*, Jonas Bispo Pessoa, Vinícios Barreto Garcia, Gerlane Coelho Bernardo Guerra, Luiz Alberto Lira Soares, Tatiane Pereira de Souza, Pedro Ros Petrovick and Aurigena Antunes de Araújo. *These authors contributed equally. July 2013. *Experimental Biology and Medicine*. DOI: 10.1177/1535370213494563. * Equal contribution.

13. A dry extract of Phyllanthus niruri protects normal cells and induces apoptosis in human liver carcinoma cells. Raimundo Fernandes de Araújo Júnior, Tatiane Pereira de Souza, Júlia Glória Lucatelli Pires, Luiz Alberto Lira Soares, Aurigena Antunes de Araújo, Pedro Ros Petrovick, Helainy Daline Oliveira Mâcedo, Ana Luiza Cabral de Sá Leitão Oliveira, Gerlane Coelho Bernardo Guerra. November 2012. *Experimental Biology and Medicine*. DOI: 10.1258/ebm.2012.012130

Patent

Araujo Junior, R. F.; Garcia, V. B.; Oliveira, A. L. C. S. L.; Gasparotto, L.H.S.; Silva, H. F. O.; Araujo, A. A. Nanoparticulated gold system and its way of obtaining applied to the immunofluorescence technique in paraffinized tissue. 2016, Brasil. Type of Patent: Innovation Privilege. Register number: BR10201602447. Registration institution: INPI - National Institute of Industrial Property. Issued date: 08/09/2021

CURRICULUM VITAE

Ana Luiza Cabral de Sá Leitão Oliveira was born in the city of Natal, Rio Grande do Norte, Brazil. She graduated with a degree in Biomedical Sciences at the Universidade Federal do Rio Grande do Norte (UFRN) in 2012, where she also completed her Master's degree in Pharmaceutical Sciences in 2014. She has worked in the Laboratory of Inflammation and Cancer Investigation with Professor Dr. Raimundo Fernandes de Araújo Júnior since the end of her graduation, who was her advisor throughout her academic period. She was a student tutor in the discipline of Pathology during her graduation studies, which touched her interest in teaching and led her to seek becoming a teacher. She was a lecturer in professional technical courses at UFRN-Escola Agrícola de Jundiaí, UFRN/EAJPRONATEC, Brazil, in 2014 and at the Universidade Potiguar, UnP, Brazil, from 2015 to 2019. Her PhD in 2015 at UFRN followed the same research line as her Master's degree, but this time working with a drug delivery system for colorectal cancer. She started an internship at the Leiden University Medical Center, the Netherlands, with Professor Dr. Luis Cruz in August 2017, working with evaluating drug delivery systems with *in vitro* and *in vivo* models. The internship partnership was renewed and transformed into an agreement between the two universities (UFRN and Leiden University) which culminated in the defense of a Doctorate degree in the Netherlands in 2022. From April 2020 to the present, Ana Luiza has been working at the Percuros B. V. company in the Netherlands as a Research Scientist.

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