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PLGA-based particulate vaccine delivery systems for immunotherapy of cancer

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List of Abbreviations

Ab	Antibody
ACN	Acetonitrile
AF488	Alexa-fluor 488
Ag	Antigen
ANOVA	Analysis of variance
APC	Antigen-presenting cell
B3Z	B3Z CD8 ⁺ T-cell hybridoma cell line, specific for the CTL epitope of ovalbumin SIINFEKL
BCA	Bicinchoninic acid protein assay
BMDC	Bone marrow-derived dendritic cells
BSA	Bovine serum albumin
CD4 ⁺ T cell	T helper cell
CD8 ⁺ T cell	Cytotoxic T lymphocyte
CFA	Complete Freund's adjuvant
CFSE	Carboxyfluorescein succinimidyl ester
CLR	C-type lectin receptor
CpG ODN	Unmethylated cytosine-phosphodiester-guanine oligodeoxynucleotide motif
CTAB	Cetyltrimethylammonium
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cell
DCM	Dichloromethane
DEAE	Diethylaminoethyl
DL	Drug loading
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOPC	Dioleoyl- glycerophosphatidylcholine
DOTAP	Dioleoyl-trimethylammonium-propane
dsRNA	Double-stranded RNA
DSS	Dioctylsulfosuccinate
EE	Encapsulation efficiency
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum
FACS	Fluorescence-activated cell sorting
FCS	Fetal calf serum

FDA	Food and drug administration
FITC	Fluorescein isothiocyanate
GM-CSF	Granulocyte-macrophage colony stimulating factor
GMP	Good manufacturing practice
gp	Glycoprotein
HBcAg	Hepatitis B core antigen
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HEPES	4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid
HLA	Human leukocyte antigen
HPLC	High-performance liquid chromatography
HPV	Human papillomavirus
i.d.	Intradermal
i.m.	Intramuscular
i.n.	Intranasal
i.p.	Intraperitoneal
IFA	Incomplete Freund's adjuvant
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subtype 1
IgG2a/b	Immunoglobulin G subtype 2a/b
IL	Interleukin
INF-g	Interferon gamma
ISCOM	Immune stimulatory complex
LE	Loading efficiency
LO	Light obscuration
LPS	Lipopolysaccharide
mAb	Monoclonal antibody
MBS	m-maleimidobenzoyl-N-hydroxysuccinimide ester
M-cell	Microfold cell
Men B	Neisseria meningitidis serotype B
MHC I/II	Major histocompatibility complex class I/II
MP	Microparticle
MPLA	Monophosphoryl lipid A
NOD	Nucleotide-binding oligomerization domain receptor
NP	Nanoparticle
o/w	Oil-in-water (emulsion)
OVA	Ovalbumin
OVA17	17-residue synthetic long peptide of ovalbumin (ISQAVHAAHAEINEAGR)

OVA24	24-residue synthetic long peptide of ovalbumin (DEVSGLEQLQESIINFEKLAAAAAK)
Pam3CSK4	Synthetic triacylated lipopeptide
PAMP	Pathogen associated molecular pattern
PBS	Phosphate buffered saline
PD-1	Programmed cell death protein 1
PDI	Polydispersity index
PD-L1/2	Programmed cell death protein 1 ligand 1/2
PEG	Poly(ethylene glycol)
PEI	Poly(ethylene imine)
PLA	Poly-lactic acid
PLA2	Phospholipase A2
PLGA	Poly(lactic-co-glycolic acid)
Poly(I:C)	Polyinosinic:polycytidylic acid
PRR	Pattern recognition receptor
RGD	Arginine-glycine-aspartate
RNA	Ribonucleic acid
RP-HPLC	Reversed-phase high-pressure liquid chromatography
s.c	Subcutaneous
SD	Standard deviation
SDS	Sodium dodecyl sulphate
SEM	Scanning electron microscopy
SEM	Standard error of the mean
SLP	Synthetic long peptide
sSLP	Soluble synthetic long peptide
SSP	Synthetic short peptide
ssRNA	single-stranded RNA
SWE	Squalene oil-in-water emulsion
TAA	Tumor associated antigens
TAP	Transporter associated with antigen processing
TCR	T cell receptor
TFA	Trifluoroacetic acid
Th	T helper
Th1	Type 1 T helper
Th2	Type 2 T helper
TLR	Toll-like receptor
TLRL	Toll-like receptor ligand
TMB	Tetramethylbenzidine
TMC	N-trimethyl chitosan

TNF	Tumor necrosis factor
TRP1/2	Tyrosinase-related protein 1/2
TT	Tetanus toxoid
w/o/w	Water-in-oil-in-water (emulsion)
Z-ave	Z-average diameter
ZP	Zeta potential

List of Publications

1. Varypataki EM*, **Silva AL***, Barnier-Quer C, Collin N, Ossendorp F, Jiskoot W, Synthetic long peptide-based vaccine formulations for induction of cell mediated immunity: a comparative study of cationic liposomes and PLGA nanoparticles, manuscript in preparation
2. Rosalia RA*, **Silva AL***, Stepanek I, van der Laan A, Oostendorp J, Jiskoot W, van der Burg SJ, Ossendorp F, Co-encapsulation of synthetic long peptide antigen and Toll like receptor 2 ligand in poly-(lactic-coglycolic-acid) particles results in sustained MHC class I cross-presentation by dendritic cells, manuscript in preparation
3. **Silva AL**, Soema P, Slütter BA, Ossendorp F, Jiskoot W, PLGA particulate delivery systems for subunit vaccines: linking particle properties to immunogenicity, accepted for publication at Human Vaccines & Immunotherapeutics
4. Rosalia RA, Cruz LJ, van Duikeren S, Tromp A, **Silva AL**, Jiskoot W, de Gruijl T, Löwik C, Oostendorp J, van der Burg SJ, Ossendorp F, CD40-targeted Dendritic Cell Delivery of PLGA-Nanoparticle vaccine induce potent anti-tumor responses, *Biomaterials*, 2015. 40: p. 88-97
5. **Silva AL***, Rosalia RA*, Varypataki E, Sibuea S, Ossendorp F, Jiskoot W, Poly-(lactic-co-glycolic-acid)-based particulate vaccines: nano-size is a key parameter for dendritic cell uptake and immune activation, *Vaccine*, 2014. 33(7): p. 847-54
6. **Silva AL**, Rosalia RA., Sazak A, Carstens M, Ossendorp F, Oostendorp J, Jiskoot W, Optimization of encapsulation of a synthetic long peptide in PLGA nanoparticles: low-burst release is crucial for efficient CD8(+) T cell activation. *Eur J Pharm Biopharm*, 2013. 83(3): p. 338-45
7. Rosalia RA, **Silva AL**, Camps M, Allam A, Jiskoot W, van der Burg SH, Ossendorp F, Oostendorp J, Efficient ex vivo induction of T cells with potent anti-tumor activity by protein antigen encapsulated in nanoparticles. *Cancer Immunol Immunother*, 2013. 62(7): p. 1161-73
8. Keijzer C, Spieringa R*, **Silva AL***, van Edena W, Jiskoot W, Verveldea L, Broerea F, PLGA nanoparticles enhance the expression of retinaldehyde dehydrogenase enzymes in dendritic cells and induce FoxP3(+) T-cells in vitro. *J Control Release*, 2013. 168(1): p. 35-40
9. Rosalia RA, Quakkelaar ED, Khan S, Redeker A, Drijfhout JW, **Silva AL**, Jiskoot W, van Hall T, van Veelen PA, Janssen G, Franken K, Cruz LJ, Tromp A, Oostendorp J, van der Burg SH, Ossendorp F, Melief CJM, Dendritic cells process synthetic long peptides better than whole protein, improving antigen presentation and T-cell activation. *Eur J Immunol*, 2013. 43(10): p. 2554-65

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Curriculum Vitae

Ana Luísa Silva was born on the tenth of February 1980 in Monterey, California, USA. In 1998 she finished high school at Escola Secundária Ibn Mucana in Alcabideche, Portugal. After graduating she studied Biological Engineering at Instituto Superior Técnico in Lisbon, Portugal. During this period she did an internship through the Erasmus program at the Università degli Studi di Milano, Italy, where she worked on the study of enantioselective hydrolysis of esters of 1,2-O-isopropylideneglycerol by enzymatic catalysis, before graduating in 2004. In 2005 she started her master's studies at Instituto Superior Técnico and performed her primary research project on enzymatic degradation of pDNA, and completed a master's thesis on the "Effect of chemical agents on plasmid resistance to nucleases" under the supervision of Prof. Dr. Gabriel Monteiro. She obtained a Master of Science degree in Biotechnology in 2007 and entered a Portuguese government program InovContacto, in which she received a grant to do an internship for 9 months at Genentech, Inc., in South San Francisco, California, USA.

In 2008 she started her PhD project on "PLGA-based particulate vaccine delivery systems for immunotherapy of cancer" under supervision of Prof. Dr. Wim Jiskoot at the Division of Drug Delivery Technology of the Leiden Academic Centre for Drug Research (LACDR) and Prof. Dr. Ferry Ossendorp at the Leiden University Medical Center (LUMC), both at Leiden University, the Netherlands. The research results of this project are described in this thesis.

