# Dendritic Cell Extracellular Vesicles

Subjects: Immunology | Oncology

Contributor: Francisco Sánchez-Madrid, Irene Fernández Delgado, Diego Calzada-Fraile

Dendritic cells have a central role in starting and regulating immune functions in anticancer responses. The crosstalk of dendritic cells with tumors and other immune cell subsets is partly mediated by extracellular vesicles (EVs) secreted by both cell types and is multidirectional. In the case of dendritic cell EVs, the presence of stimulatory molecules and their ability to promote tumor antigen-specific responses, have raised interest in their uses as therapeutics vehicles.

Keywords: Dendritic Cell Extracellular Vesicles ; Cancer ; immune system

## 1. Introduction

Cancer is a very heterogeneous disease that can develop in almost any tissue due to the tumorigenic transformation of normal cells. Malignant cell transformation is a multi-step, diverse process that might be instigated by genetic factors. Hanahan and Weinberg outlined the six core “hallmarks of cancer” placing the spotlight on the role of the tumor microenvironment in malignant cell progression [1].

Cancer thrives after escaping control checkpoints. The immune system exerts one of the main defense mechanisms against malignant cells via immune surveillance and specific antitumor immune responses. This comprises two arms: innate immune cells that define a first rapid line of defense and adaptive immune cells, which drive an antigen-specific response that includes the development of long-term memory. However, memory traits have also been observed in the innate compartment based on epigenetic and metabolic reprogramming of cells, the so-called “trained immunity” [2]. Among innate immune cells, the main players are phagocytic cells such as neutrophils, monocytes, and macrophages; professional antigen presenting cells (APCs) such as dendritic cells (DCs), or cell slayers such as natural killers (NKs). Adaptive immune cells include antibody (Ab)-producers B lymphocytes; $CD8^+$ cytotoxic T cells; or helper cells, which include the family of $CD4^+$ T cells ($Th_1$, $Th_2$, $Th_{17}$, $T_{reg}$, and others). Around and within tumor environment, innate and adaptive immune cells are crucial players [3].

Immature DCs switch to an activated state through a maturation process after stimulation by a danger signal, such as sensing a pathogen-derived molecule, or tissue damage [4]. These cells infiltrate the tumor and recruit effector cells. DCs represent the most effective APCs able to prime naïve T cells and induce an effective antigen-specific antitumor defense. They include a vast variety of cellular types with diverse functions depending on their origin, location, and properties. For instance, DCs can be subdivided into: (i) conventional DCs (cDCs), either resident of lymphoid tissues or migratory, where we can find cDC1 required more for pathogen/tumor immune responses or cDC2 more focus on major histocompatibility complex (MHC)-II based responses; (ii) plasmacytoid DCs, main producers of type 1 interferon (IFN), (iii) tissue-specific DCs such as Langerhans cells (LCs) or dermal DCs (dDCs) and (iv) monocytic-derived DCs (moDCs), producers of tumor necrosis factor (TNF)-α and inducible nitric oxide synthase (iNOS) [5]. In particular, cDC1 are critical in tumor surveillance, antitumor antigen-specific T cell responses, responsiveness to immunotherapies, and are associated with increased patient survival [6].

Extracellular vesicles (EVs) are secreted by cells to the extracellular milieu [7] and comprise mainly three subgroups depending on their origin: (i) shedding vesicles, generated by evagination of the plasma membrane; (ii) exosomes, generated at the multivesicular bodies and secreted by its fusion with the plasma membrane; and (iii) apoptotic vesicles [8][9][10]. These vesicles are constituted by a lipid bilayer containing an assortment of proteins, lipids, metabolites, and nucleic acids, the latter including microRNA (miRNA), mRNA, long non-coding RNA (lncRNA), DNA and mitochondrial DNA (mitDNA) [10][11][12][13]. Although their biogenesis is still under study, there is evidence of an active sorting process of molecules into these vesicles as its cargo is not a mere reflection of the cell content [10][14][15]. For instance, sorting mechanisms include tetraspanins, lipids, specific proteins, post-translational modifications, or endosomal sorting complexes required for transport (ESCRT)-dependent processes [14][16][17][18][19]. Their functions include a variety of cellular processes, but these vesicles are specialized in intercellular communication [20][21]. EVs can function as autocrine, paracrine, or endocrine entering into circulation. Once they reach their final destination, the mechanisms underlying their

internalization and signaling processes remain still under consideration [7][8][10]. Almost any type of cell can secrete EVs, including malignant cells and immune cells [8][10][11][21]. There are specific markers for each type of vesicle, specific for a certain cell type or even to distinguish between types of vesicles from the same cell type [21][22][23][24]. Besides, EVs can be detected in any type of biological fluid [21][22]. For example, as EVs from malignant cells convey tumor molecules, they represent good tumor biomarkers and excellent liquid tumor biopsies [25][26]. Interestingly, in cancer patients, the amount of serum-EVs were shown to correlate with a poor prognosis [27]. Vesicle secretion and size heterogeneity has made it difficult to decipher their precise origin and functions, generating some controversy [28][29][30][31][32].

## 2. Modulation of Antitumor Immunity by Dendritic Cells (DCs)-Derived Extacellular Vesicles (EVs)

### 2.1. DCs-Derived EVs (DEVs)

Immune cells can secrete immunologically active EVs [8]. One of the first studies of vesicles in immune responses described the role of B cell-EVs carrying MHC-II molecules on their surface in driving T cell proliferation [33]. Since then, the number of publications on immune cell-derived vesicles functions has not ceased to grow due to their potential in human immunotherapies, for instance against cancer. Among innate immune cells, we will focus our attention on EVs derived from DCs (DEVs) [34]. At the end of the 90s, Zitvogel and colleagues showed that DEVs convey tumor-associated antigens (TAAs) promoting antitumor immunity by effector T cells [35]. In particular, DEVs contain a specific repertoire of molecules like T cell co-stimulatory molecules (CD86, CD80, CD40) [36][37], antigen presenting molecules (MHC-II, MHC-I) [36][37][38], adhesion molecules (Integrins, intercellular adhesion molecule 1 (ICAM-1), dendritic cell-specific intercellular adhesion molecule-3-Grabbing non-integrin (DC-SIGN)) [39], NK modulation molecules (TNF-α, interleukin 15 receptor α (IL-15Rα), NKG2D-L) [40][41] and the EV markers such as tetraspanins (CD9, CD81, CD63), ESCRT complex proteins (Tumor susceptibility gene 101 (TSG101), ALG-2-interacting protein X (ALIX)), heat shock proteins (HSC73, HSP84) and others (SYNTENIN-1, ACTIN) [37]. The amount of MHC molecules or co-stimulatory molecules depends on the physiological state of the DC [38][42][43]. In fact, EVs secreted from DCs can transfer functional MHC-I-peptide complexes to other DCs [44]. Not only DEVs induce stimulation of naïve $CD4^+$ T cells, but also these EVs are also used by mature DCs as a source of tumor antigens [43][45]. Apart from proteins, nucleic acids sorted within DEVs play an important role in the regulation of immune responses, in particular miRNAs both from immature and mature DCs [46][47][48]. The secretion of these vesicles by DCs can be altered upon exposure to different stimuli [49][50]. Highlighting the heterogeneous nature of these vesicles, different subtypes of DEVs could also be found, each of which could perform a variety of functions [50][51].

### 2.2. DEVs Function

One of the main functions of DEVs is T cell activation:

- EVs from an antigen-loaded DC bearing tumor antigens may promote $CD4^+$ and $CD8^+$ T cell responses by direct antigen presentation, which leads to tumor growth suppression [35][36][52] with increased efficiency in the case of mature DC-derived EVs [39].

- Moreover, by coating DCs with the pMHC-loaded EVs, a process known as MHC cross-dressing, T cell response is reinforced and amplified [53][54].

- DEVs can also be internalized by other DCs as a source of exogenous peptide-loaded MHC (pMHC), which may be subsequently presented to naïve, primed, or memory T cells [43][44][45][55][56][57]. This process has a special relevance in organ transplantation as acceptor DCs incorporate donor-DEVs to stimulate allospecific T cells [58]. A mechanism and source of tumor antigens is the internalization of EVs containing the full antigen or peptide, that would be presented later by endogenous MHC-I molecules at the acceptor cell in a process called cross-presentation [59]. In fact, EVs loaded with the whole antigen are more efficient in antigen presentation than EVs bearing only pMHC [60][61]. These antigen-loaded EVs elicit a Th1 $CD4^+$ and $CD8^+$ T cell response dependent on B cell activation [62][63]. This response might also be enhanced by the presence of CD80 and ICAM-1 in those EVs [39]. Besides, bystander T cells can promote DC maturation in the absence of innate stimuli [64][65][66], which is also reflected in DEVs supporting subsequent specific antigen T cell activation [67].

- In addition, DCs can incorporate pMHC-loaded vesicles from other cell origins, such as epithelial cells, to potentiate antigen presentation to T cells [68].

Antigen-loaded DEVs can play many other functions in addition to modulating T cell responses, such as promoting humoral immunity [69][70]. DEVs also contain NKG2D-L and IL-15Rα, contributing to NK cell activation and proliferation [41]. DEVs can directly activate NK cells via TNF-α as they display it on their surface together with FasL and TRAIL. These NK

cell responses, along with the apoptotic signaling, contribute to tumor cell removal [71]. Furthermore, EVs from heat shocked-activated DCs bear BAT3, the ligand for NKp30, mediating cytokine release and NK cell cytotoxicity [72].

Therefore, DEVs entail an important tool to elicit the immune response against malignant cells. These vesicles can boost both T cell and NK responses, whose cytotoxicity leads to tumor cell killing [34][40]. Other DCs can internalize or be coated with DEVs enhancing the antitumor response [43][54].

### 2.3. Cancer Counteracts DC Function

Immune evasion is one of the emerging hallmarks for cancer [1]. Tumor cells manage to escape immune responses, particularly inhibiting T cell activation and DC differentiation [73]. Notably, tumor cells can shed a large amount of EVs, highlighting the importance of vesicle secretion during tumor development [74][75]. Tumor-derived EVs (TDEVs) can mediate many aspects of the immune response [76]. TDEVs can alter the microenvironment of the tumor promoting both pro/anti-inflammatory responses on monocytes, macrophages, and DCs, as well as anti-inflammatory responses acting on NKs and $T_{reg}$, thus modulating angiogenesis, invasion, apoptosis, and metastasis [76][77]. TDEVs contain a repertoire of proteins, DNA and miRNAs that alter DC function and differentiation, and lead to a change in the immune response, thus favoring or hampering tumor progression. Therefore, the design of DC-based immunotherapies must take into account the conundrum that DC per se might fight the tumor, but TDEVs at the tumor microenvironment might sway DCs function into a pro-tumor phenotype.

Tumors have managed to contain a repertoire of mechanisms to evade any antitumoral response. In particular, the importance of TDEVs on these processes is remarkable. TDEVs can hinder many aspects of antitumor immune response, from increasing suppressor cell populations, like myeloid-derived suppressor cells (MDSCs), to decreasing antigen presentation processes. On the contrary, DCs can take advantage of TDEVs as they convey TAAs, which might serve as a source for direct or indirect presentation mechanisms. However, this remains to be fully characterized, especially in the case of direct TAAs presentation carried by DEVs. Finally, diversity in EVs methodology and DC sources used in these studies may pose a confounding factor when interpreting these data.

## 3. DEV-Based Cancer Therapeutics

The fine modulation of the immune responses that EVs are able to perform, as well as their abilities for shuttling different biomolecules, including proteins that may serve as antigens to mount an immune response, have made EVs interesting candidates for different uses in therapeutic and prevention contexts where the immune system has a major role.

A pioneering study using autologous DEVs showed rejection of tumors in mice when loaded with tumor peptides and therefore used as a cell-free vaccine [35]. Driven by these observations, several in vivo and clinical trials have followed and explored the use of EVs (more prominently DEVs) as potential immunotherapeutic agents in cancer (reviewed in [78][79]). In this section, we will focus on the use of DEVs as therapeutic agents in the context of cancer. Importantly, we differentiate between vaccination approaches, when EVs are loaded with tumor antigens in order to elicit (tumor) antigen-specific immune responses, or immunotherapies if they are not loaded with tumor antigens or their therapeutic effects are based on immunomodulation independently on whether they improve a later antitumoral antigen-specific immune response.

### 3.1. DEV-Based Tumor Vaccines

Several sources of EVs have been used as potential tumor vaccine candidates. However, DEVs are the most interesting EVs to activate specific immune responses because: (1) they are antigen-presenting platforms as they contain MHC-I and-II or CD1 loaded with tumor peptides as well as co-stimulatory molecules (CD80, CD86) ([37][39][80][81] reviewed in [82]); and (2) because the activation state of their cellular source can be manipulated. Due to the feasibility of large production of DCs for DEVs generation, most studies that explored the use of DEVs in antitumor settings in ex vivo, in vitro and in vivo have used murine bone-marrow-derived DCs (BMDCs) as a source for DEVs production. These DEVs have been loaded with different TAAs to mount specific T cell responses against tumors (examples can be found in Figure 1A). In these cases, antigen-loaded DEVs were able to increase overall survival and reduce tumor growth. These effects were accompanied by a potent activation of both $CD4^+$ and $CD8^+$ T cells responses. Also, evidence has pointed out that the use of activated DC as producers of DEVs increases the eficacy of DEVs when used as cancer vaccines [83]. Owing to this, several studies have explored the use of DEVs coming from DCs stimulated with TLR ligands [84][85][86].

**Figure 1.** Therapeutic and prophylactic applications of DEVs in cancer. Mice and human DEVs have been used in antitumor studies as therapeutic or prophylactic agents. (**A**) DEV-based cancer vaccines have been designed by loading DEVs with peptide-loaded MHC (pMHC) molecules, tumor proteins and lysates, or mRNAs that encode neoantigens with the goal to mount antigen (Ag)-specific antitumor responses. (**B**) DEVs-based anti-pathogen vaccine platforms for cancer prevention have been designed either by natural-occurring antigen loading to DEVs or by fusing antigens to DEV proteins. Also, their ability as adjuvant carriers and antigen-DEV formulations has been explored to increase vaccine efficacy. In addition, DEVs are a potential platform for mRNA vaccine delivery. (**C**) DEVs have been used as immunotherapeutic agents by exploiting their immune stimulatory properties. DEVs can directly stimulate innate cells such as natural killer T cells (NKT), NK, and γδ T cells or modulate the immune response indirectly by the delivery of miRNAs; or induce tumor cell apoptosis via ligand interaction or targeted delivery of chemotherapeutics. MAGE, melanoma antigen gene; OVA, ovalbumin; E7, human papillomavirus E7 protein; HBV, hepatitis B virus; HBsAg, surface antigen of the HBV; Nef, negative regulatory factor from human immunodeficiency virus; α-GalCer, α-galactosylceramide; poly(I:C), polyinosinic:polycytidylic acid; FasL, Fas ligand; TNF, tumor necrosis factor; LAMP2b–iRGD, lysosome-associated membrane protein 2 (LAMP2b) fused to the integrin-specific peptide iRGD.

### 3.2. DEV as Vaccines for Oncogenic Pathogens

In all these cases, DEVs are used as therapeutic rather than prophylactic vaccines. Indeed, the prophylactic use of DEVs against cancer is largely unexplored because intervention is usually used when the disease appears. However, many pathogens have been described to induce carcinogenesis by direct or indirect mechanisms. Hence, implementation of prophylactic vaccines that target oncopathogens constitute a potential health benefit. EVs in general have been explored as a novel vaccine platform for infectious diseases to a lower extent than cancer vaccines, and no clinical trial have been performed to date. In some cases, EVs have shown increased efficacy than traditional vaccine formulations against pathogens. Targeting of pathogen proteins to EVs endowed efficient antigen-specific cellular [87] and humoral immune responses [88]. Other strategies that use DEVs in vaccination are depicted in Figure 1B.

### 3.3. DEV-based Immunothreapies

DEVs can modulate T cell activation as DEVs coming from human moDCs that were not exposed to a specific antigen could stimulat $CD4^+$ T cell ex vivo generating a Th1-type response when using small DEVs; and towards Th2 when using large DEVs from immature cells [50]. Also, DEVs can stimulate NK cell functions. Using murine BMDC DEVs administered intradermally to mice, NK cell proliferation and activation that mediated by IL-15Ra and NKG2D ligands was observed [89]. Other immunotherapeutic strategies for the use of DEVs are depcited in Figure 1C.

### 3.4. Clincal Trials Using DEVs

To date, four phase I and one phase II clinical trials have been performed using DEVs as immunotherapeutic agents.The outcome of this trials in summarized in Table 1.

**Table 1.** Clinical trials using DEVs performed to date and their main immune and clinical outcomes.

| Targeted Tumor Type | Phase of Trial | n [1] | Treatment | Loaded Antigen | Immune Effects | Clinical Outcome | Ref. |
|---|---|---|---|---|---|---|---|
| NSCLC (stage IIIb and IV) | I | 13 (9) | DEVs from moDC | MAGE-A3, -A4, -A10, and MAGE-3DPO4 peptides + CMV and tetanus toxoid peptide (direct or indirect loading) | DTH reactivity against MAGE peptides in 3/9.<br>MAGE-specific T cell responses in 1/3.<br>NK lytic activity in 2/4.<br>CMV responses.<br>Increase of $T_{regs}$ in 2/3. | Well tolerated.<br>Mild adverse events.<br>Stabilization after progression in 2/9. | [90] |
| Melanoma (stage IIIb and IV) | I | 15 | DEVs from moDC | $MAGE3_{168–176}$ and $MAGE3_{247–258}$ | Specific T cell responses in peripheral blood not detected.<br>One case of tumor infiltration of activated T cells.<br>NK cell number and NKG2D function recovered in 7/14.<br>NKG2D expression in $CD8^+$ T cells in 6/14. | No toxicity (mild adverse events).<br>One patient exhibited a partial response. | [89] [91] |
| Colorectal cancer (stage III or IV) | I | 40 | AEVs + GM-CSF | Contain CEA | DTH response as well as a CEA-specific CTL cell response | Well tolerated. Stabilization in 1 and minor response in 1. | [92] |
| NSCLC (stage IIIb and IV) | II | 26 (22) | DEVs from IFNγ-matured moDC | MAGE-A1, MAGE-A3, NY-ESO-1, Melan-A/MART1, MAGE-A3-DP04 and EBV peptides. | Tumor antigen-specific T cell responses only in 2/8.<br>Increased NKp30-dependent NK cell functions. | Stabilization with continuation of injections in 7.<br>Long-term stabilization in 1.<br>Hepatotoxicity in 1. | [93] |

## The Future of DEVs in Vaccination Approaches

The increased efficacy and versatility of EV-based vaccines have made them potential candidates for rapid development of vaccines against emerging infections [94][95]. For example, EVs targeting has not only increased immunogenicity of EV-based vaccines as discussed before, but it has also been shown to improve the humoral responses in adenoviral vector vaccines, including ChAdOx1, one of the candidates leading the race for a SARS-CoV-2 vaccine [96]. Interestingly, five registered human clinical trials are exploring the use of EVs as therapeutics against COVID-19. Besides, EV-based

vaccines may contribute to the new era of mRNA vaccination for emerging pathogens and personalized cancer vaccines via delivery of mRNAs encoding neoantigens [97][98]. Also, the classical rationale behind the use of DEVs as tumor vaccines or vaccines for oncogenic pathogens relies on the inducing antigen-specific immune responses and adaptive memory. However, the broadening of the concept of vaccination with the appearance of the first generation of trained immunity-based vaccines [99] opens new horizons in exploiting this new arm of the immune system as a new source of therapeutic strategies for immunotherapy and cancer vaccines.

## 4. Conclusion

In the context of tumor development, EVs are present in the tumor microenvironment and are secreted by a variety of cell types. On the one side, immune cells produce EVs to fight against tumor progression and metastasis. As illustrated before, DCs, in particular, can secrete EVs to increase the T cell response by enhancing antigen presentation by a diversity of mechanisms. On the other side, malignant cells produce EVs to escape immune responses and virtually, they can interact with every type of immune cell. Additionally, the great ability of DEVs as immune modulators and kick-starters of robust antigen-specific T cell responses and NK cell responses have allowed the use of DEVs in different immunotherapeutic settings: both as novel and effective cancer vaccines and cancer immunotherapies (Figure 1). Several in vivo studies as well as clinical trials support the increased efficacy of the use of DEVs as cancer vaccines compared to DC-based vaccines. However, the prophylactic use of DEVs as a novel and versatile vaccine platform against infectious agents, including oncopathogens, is still at its inception. Combining the use of DEVs and emerging technologies such as mRNA vaccination or the exploitation of trained immunity mechanisms will push forward the frontier of tumor vaccination approaches.

### References


1. Douglas Hanahan; Robert A. Weinberg; Hallmarks of Cancer: The Next Generation. *Cell* **2011**, *144*, 646-674, 10.1016/j.cell.2011.02.013.
2. Mihai G. Netea; Leo A. B. Joosten; Eicke Latz; Kingston H. G. Mills; Gioacchino Natoli; Hendrik G. Stunnenberg; Luke A. J. O'Neill; Ramnik J. Xavier; Trained immunity: A program of innate immune memory in health and disease. *Science* **2016**, *352*, aaf1098-aaf1098, 10.1126/science.aaf1098.
3. Hugo Gonzalez; Catharina Hagerling; Zena Werb; Roles of the immune system in cancer: from tumor initiation to metastatic progression. *Genes & Development* **2018**, *32*, 1267-1284, 10.1101/gad.314617.118.
4. Jacques Banchereau; Ralph M. Steinman; Dendritic cells and the control of immunity. *Nature* **1998**, *392*, 245-252, 10.1038/32588.
5. Elodie Segura; Review of Mouse and Human Dendritic Cell Subsets. *Bioinformatics in MicroRNA Research* **2016**, *1423*, 3-15, 10.1007/978-1-4939-3606-9_1.
6. Jan P. Böttcher; Caetano Reis E Sousa; The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. *Trends in Cancer* **2018**, *4*, 784-792, 10.1016/j.trecan.2018.09.001.
7. Guillaume Van Niel; Gisela D'angelo; Graça Raposo; Shedding light on the cell biology of extracellular vesicles. *Nature Reviews Molecular Cell Biology* **2018**, *19*, 213-228, 10.1038/nrm.2017.125.
8. Clotilde Théry; Matias Ostrowski; Elodie Segura; Membrane vesicles as conveyors of immune responses. *Nature Reviews Immunology* **2009**, *9*, 581-593, 10.1038/nri2567.
9. Graça Raposo; Willem Stoorvogel; Extracellular vesicles: Exosomes, microvesicles, and friends. *Journal of Cell Biology* **2013**, *200*, 373-383, 10.1083/jcb.201211138.
10. Marina Colombo; Graça Raposo; Clotilde Théry; Biogenesis, Secretion, and Intercellular Interactions of Exosomes and Other Extracellular Vesicles. *Annual Review of Cell and Developmental Biology* **2014**, *30*, 255-289, 10.1146/annurev-cellbio-101512-122326.
11. Cristina Gutiérrez-Vázquez; Carolina Villarroya-Beltri; María Mittelbrunn; F. Sanchez-Madrid; Transfer of extracellular vesicles during immune cell-cell interactions. *Immunological Reviews* **2012**, *251*, 125-142, 10.1111/imr.12013.
12. Daniel Torralba; Francesc Baixauli; F. Sanchez-Madrid; Mitochondria Know No Boundaries: Mechanisms and Functions of Intercellular Mitochondrial Transfer. *Frontiers in Cell and Developmental Biology* **2016**, *4*, 107, 10.3389/fcell.2016.00107.
13. Michel Record; Kevin Carayon; Marc Poirot; Sandrine Silvente-Poirot; Exosomes as new vesicular lipid transporters involved in cell–cell communication and various pathophysiologies. *Biochimica et Biophysica Acta (BBA) - Molecular*

*and Cell Biology of Lipids* **2014**, *1841*, 108-120, 10.1016/j.bbalip.2013.10.004.

14. Joanna Kowal; Mercedes Tkach; Clotilde Théry; Biogenesis and secretion of exosomes. *Current Opinion in Cell Biology* **2014**, *29*, 116-125, 10.1016/j.ceb.2014.05.004.
15. Nina Pettersen Hessvik; Alicia Llorente; Current knowledge on exosome biogenesis and release. *Cellular and Molecular Life Sciences* **2017**, *75*, 193-208, 10.1007/s00018-017-2595-9.
16. Carolina Villarroya-Beltri; Francesc Baixauli; Cristina Gutiérrez-Vázquez; Francisco Sánchez-Madrid; María Mittelbrunn; Sorting it out: Regulation of exosome loading. *Seminars in Cancer Biology* **2014**, *28*, 3-13, 10.1016/j.semcancer.2014.04.009.
17. Olga Moreno-Gonzalo; Irene Fernández-Delgado; Francisco Sánchez-Madrid; Post-translational add-ons mark the path in exosomal protein sorting. *Cellular and Molecular Life Sciences* **2017**, *75*, 1-19, 10.1007/s00018-017-2690-y.
18. Sushma Anand; Monisha Samuel; Sharad Kumar; Suresh Mathivanan; Ticket to a bubble ride: Cargo sorting into exosomes and extracellular vesicles. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **2019**, *1867*, 140203, 10.1016/j.bbapap.2019.02.005.
19. Olga Moreno-Gonzalo; Carolina Villarroya-Beltri; F. Sanchez-Madrid; Post-Translational Modifications of Exosomal Proteins. *Frontiers in Immunology* **2014**, *5*, 1-7, 10.3389/fimmu.2014.00383.
20. Mikael Simons; Graça Raposo; Exosomes – vesicular carriers for intercellular communication. *Current Opinion in Cell Biology* **2009**, *21*, 575-581, 10.1016/j.ceb.2009.03.007.
21. María Yáñez-Mó; Pia Siljander; Zoraida Andreu; Apolonija Bedina Zavec; Francesc E. Borràs; Edit I. Buzas; Krisztina Buzas; Enriqueta Casal; Francesco Cappello; Joana Carvalho; et al. Biological properties of extracellular vesicles and their physiological functions. *Journal of Extracellular Vesicles* **2015**, *4*, 27066, 10.3402/jev.v4.27066.
22. Oscar P. B. Wiklander; Joel Z. Nordin; Aisling O'loughlin; Ylva Gustafsson; Giulia Corso; Imre Mäger; Pieter Vader; Yi Lee; Helena Sork; Yiqi Seow; et al. Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting. *Journal of Extracellular Vesicles* **2015**, *4*, 26316, 10.3402/jev.v4.26316.
23. Marina Colombo; Catarina Moita; Guillaume Van Niel; Joanna Kowal; James Vigneron; Philippe Benaroch; Nicolas Manel; Luis F. Moita; Clotilde Théry; Graça Raposo; et al. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. *Journal of Cell Science* **2013**, *126*, 5553-5565, 10.1242/jcs.128868.
24. Angélique Bobrie; Marina Colombo; Sophie Krumeich; Graça Raposo; Clotilde Théry; Diverse subpopulations of vesicles secreted by different intracellular mechanisms are present in exosome preparations obtained by differential ultracentrifugation. *Journal of Extracellular Vesicles* **2012**, *1*, 18397, 10.3402/jev.v1i0.18397.
25. Nobuyoshi Kosaka; Haruhisa Iguchi; Takahiro Ochiya; Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. *Cancer Science* **2010**, *101*, 2087-2092, 10.1111/j.1349-7006.2010.01650.x.
26. Irina Nazarenko; Extracellular Vesicles: Recent Developments in Technology and Perspectives for Cancer Liquid Biopsy. *Bioinformatics in MicroRNA Research* **2019**, *215*, 319-344, 10.1007/978-3-030-26439-0_17.
27. Patrick S. Mitchell; Rachael K. Parkin; Evan M. Kroh; Brian R. Fritz; Stacia K. Wyman; Era L. Pogosova-Agadjanyan; Amelia Peterson; Jennifer Noteboom; Kathy C. O'briant; April Allen; et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proceedings of the National Academy of Sciences* **2008**, *105*, 10513-10518, 10.1073/pnas.0804549105.
28. Fatemeh Momen-Heravi; Leonora Balaj; Sara Alian; John Etigges; Vasilis Etoxavidis; Maria Ericsson; Robert J. Distel; Alexander R. Ivanov; Johan Skog; Winston Patrick Kuo; et al. Alternative Methods for Characterization of Extracellular Vesicles. *Frontiers in Physiology* **2012**, *3*, 354, 10.3389/fphys.2012.00354.
29. Huilin Shao; Hyungsoon Im; Cesar M. Castro; Xandra Breakefield; Ralph Weissleder; Hakho Lee; New Technologies for Analysis of Extracellular Vesicles. *Chemical Reviews* **2018**, *118*, 1917-1950, 10.1021/acs.chemrev.7b00534.
30. Mercedes Tkach; Joanna Kowal; Clotilde Théry; Why the need and how to approach the functional diversity of extracellular vesicles. *Philosophical Transactions of the Royal Society B: Biological Sciences* **2017**, *373*, 20160479, 10.1098/rstb.2016.0479.
31. Jan Lötvall; Andrew F. Hill; Fred Hochberg; Edit I. Buzás; Dolores Di Vizio; Christopher Gardiner; Yong Song Gho; Igor V. Kurochkin; Suresh Mathivanan; Peter Quesenberry; et al. Minimal experimental requirements for definition of extracellular vesicles and their functions: a position statement from the International Society for Extracellular Vesicles. *Journal of Extracellular Vesicles* **2014**, *3*, 26913, 10.3402/jev.v3.26913.
32. Clotilde Théry; Kenneth W. Witwer; Elena Aikawa; Maria Jose Alcaraz; Johnathon D Anderson; Ramaroson Andriantsitohaina; Anna Antoniou; Tanina Arab; Fabienne Archer; Georgia K Atkin-Smith; et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular

Vesicles and update of the MISEV2014 guidelines. *Journal of Extracellular Vesicles* **2018**, *7*, 1535750, 10.1080/20013078.2018.1535750.

33. G Raposo; H W Nijman; W Stoorvogel; R Liejendekker; C V Harding; C J Melief; H J Geuze; B lymphocytes secrete antigen-presenting vesicles.. *The Journal of Experimental Medicine* **1996**, *183*, 1161-1172, 10.1084/jem.183.3.1161.
34. Joanna Kowal; Mercedes Tkach; Dendritic cell extracellular vesicles. *International Review of Cell and Molecular Biology* **2019**, *349*, 213-249, 10.1016/bs.ircmb.2019.08.005.
35. Laurence Zitvogel; Armelle Regnault; Anne Lozier; Joseph Wolfers; Caroline Flament; Danielle Tenza; Paola Ricciardi-Castagnoli; Graça Raposo; Sebastian Amigorena; Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. *Nature Medicine* **1998**, *4*, 594-600, 10.1038/nm0598-594.
36. C. Admyre; Sara M. Johansson; Staffan Paulie; Susanne Gabrielsson; Direct exosome stimulation of peripheral humanT cells detected by ELISPOT. *European Journal of Immunology* **2006**, *36*, 1772-1781, 10.1002/eji.200535615.
37. Clotilde Théry; Muriel Boussac; Philippe Véron; Paola Ricciardi-Castagnoli; Graça Raposo; Jerôme Garin; Sebastian Amigorena; Proteomic Analysis of Dendritic Cell-Derived Exosomes: A Secreted Subcellular Compartment Distinct from Apoptotic Vesicles. *The Journal of Immunology* **2001**, *166*, 7309-7318, 10.4049/jimmunol.166.12.7309.
38. Sonja I. Buschow; Esther N. M. Nolte-'T Hoen; Guillaume Van Niel; Maaike S. Pols; Toine Ten Broeke; Marjolein Lauwen; Ferry Ossendorp; Cornelis J. M. Melief; Graça Raposo; Richard Wubbolts; et al. MHC II in Dendritic Cells is Targeted to Lysosomes or T Cell-Induced Exosomes Via Distinct Multivesicular Body Pathways. *Traffic* **2009**, *10*, 1528-1542, 10.1111/j.1600-0854.2009.00963.x.
39. Elodie Segura; Carole Nicco; Bérangère Lombard; Philippe Véron; Graça Raposo; Frédéric Batteux; Sebastian Amigorena; Clotilde Théry; ICAM-1 on exosomes from mature dendritic cells is critical for efficient naive T-cell priming. *Blood* **2005**, *106*, 216-223, 10.1182/blood-2005-01-0220.
40. Katrin S. Reiners; Juliane Daßler-Plenker; Christoph Coch; Elke Pogge Von Strandmann; Role of Exosomes Released by Dendritic Cells and/or by Tumor Targets: Regulation of NK Cell Plasticity. *Frontiers in Immunology* **2014**, *5*, 91, 10.3389/fimmu.2014.00091.
41. Sophie Viaud; Magali Terme; Caroline Flament; Julien Taieb; Fabrice André; Sophie Novault; Bernard Escudier; Caroline Robert; Sophie Caillat-Zucman; Thomas Tursz; et al. Dendritic Cell-Derived Exosomes Promote Natural Killer Cell Activation and Proliferation: A Role for NKG2D Ligands and IL-15Rα. *PLOS ONE* **2009**, *4*, e4942, 10.1371/journal.pone.0004942.
42. Toine Ten Broeke; Guillaume Van Niel; Marca H.M. Wauben; Richard Wubbolts; Willem Stoorvogel; Endosomally Stored MHC Class II Does Not Contribute to Antigen Presentation by Dendritic Cells at Inflammatory Conditions. *Traffic* **2011**, *12*, 1025-1036, 10.1111/j.1600-0854.2011.01212.x.
43. Elodie Segura; Sebastian Amigorena; Clotilde Théry; Mature dendritic cells secrete exosomes with strong ability to induce antigen-specific effector immune responses. *Blood Cells, Molecules, and Diseases* **2005**, *35*, 89-93, 10.1016/j.bcmd.2005.05.003.
44. Fabrice André; Nathalie Chaput; Nöel E. C. Schartz; Caroline Flament; Nathalie Aubert; Jacky Bernard; François Lemonnier; Graça Raposo; Bernard Escudier; Di-Hwei Hsu; et al. Exosomes as Potent Cell-Free Peptide-Based Vaccine. I. Dendritic Cell-Derived Exosomes Transfer Functional MHC Class I/Peptide Complexes to Dendritic Cells. *The Journal of Immunology* **2004**, *172*, 2126-2136, 10.4049/jimmunol.172.4.2126.
45. Clotilde Théry; Livine Duban; Elodie Segura; Philippe Véron; Olivier Lantz; Sebastian Amigorena; Indirect activation of naïve CD4+ T cells by dendritic cell–derived exosomes. *Nature Immunology* **2002**, *3*, 1156-1162, 10.1038/ni854.
46. Angela Montecalvo; Adriana T. Larregina; William J. Shufesky; Donna Beer Stolz; Mara L. G. Sullivan; Jenny M. Karlsson; Catherine J. Baty; Gregory A. Gibson; Geza Erdos; Zhiliang Wang; et al. Mechanism of transfer of functional microRNAs between mouse dendritic cells via exosomes. *Blood* **2012**, *119*, 756-766, 10.1182/blood-2011-02-338004.
47. Margaret Alexander; Ruozhen Hu; Marah C. Runtsch; Dominique A. Kagele; Timothy L. Mosbruger; Tanya Tolmachova; Miguel C. Seabra; June L. Round; Diane M. Ward; Ryan M. O'connell; et al. Exosome-delivered microRNAs modulate the inflammatory response to endotoxin. *Nature Communications* **2015**, *6*, 7321, 10.1038/ncomms8321.
48. Tom A. P. Driedonks; Susanne G. Van Der Grein; Yavuz Ariyurek; Henk P. J. Buermans; Henrike Jekel; Franklin W. N. Chow; Marca H. M. Wauben; Amy H. Buck; Peter A. C. 'T Hoen; Esther N. M. Nolte-'T Hoen; et al. Immune stimuli shape the small non-coding transcriptome of extracellular vesicles released by dendritic cells. *Cellular and Molecular Life Sciences* **2018**, *75*, 3857-3875, 10.1007/s00018-018-2842-8.
49. Cinzia Pizzirani; Davide Ferrari; Paola Chiozzi; Elena Adinolfi; Dorianna Sandonà; Erika Savaglio; Francesco Di Virgilio; Stimulation of P2 receptors causes release of IL-1β–loaded microvesicles from human dendritic cells. *Blood* **2006**, *109*, 3856-3864, 10.1182/blood-2005-06-031377.

50. Mercedes Tkach; Joanna Kowal; Andres E Zucchetti; Lotte Enserink; Mabel Jouve; Danielle Lankar; Michael Saitakis; Lorena Martin-Jaular; Clotilde Théry; Qualitative differences in T-cell activation by dendritic cell-derived extracellular vesicle subtypes. *The EMBO Journal* **2017**, *36*, 3012-3028, 10.15252/embj.201696003.

51. Joanna Kowal; Guillaume Arras; Marina Colombo; Mabel Jouve; Jakob Paul Morath; Bjarke Primdal-Bengtson; Florent Dingli; Damarys Loew; Mercedes Tkach; Clotilde Théry; et al. Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes. *Proceedings of the National Academy of Sciences* **2016**, *113*, E968-E977, 10.1073/pnas.1521230113.

52. Marthe F.S. Lindenbergh; Willem Stoorvogel; Antigen Presentation by Extracellular Vesicles from Professional Antigen-Presenting Cells. *Annual Review of Immunology* **2018**, *36*, 435-459, 10.1146/annurev-immunol-041015-055700.

53. Linda M. Wakim; Michael J. Bevan; Cross-dressed dendritic cells drive memory CD8+ T-cell activation after viral infection. *Nature* **2011**, *471*, 629-632, 10.1038/nature09863.

54. Furong Zeng; Adrian E. Morelli; Extracellular vesicle-mediated MHC cross-dressing in immune homeostasis, transplantation, infectious diseases, and cancer. *Seminars in Immunopathology* **2018**, *40*, 477-490, 10.1007/s00281-018-0679-8.

55. Hélène Vincent-Schneider; Pamela Stumptner-Cuvelette; Danielle Lankar; Sabine Pain; Graça Raposo; Philippe Benaroch; Christian Bonnerot; Exosomes bearing HLA-DR1 molecules need dendritic cells to efficiently stimulate specific T cells. *International Immunology* **2002**, *14*, 713-722, 10.1093/intimm/dxf048.

56. Siguo Hao; Ou Bai; Fang Li; Jinying Yuan; Suzanne Laferte; Jim Xiang; Mature dendritic cells pulsed with exosomes stimulate efficient cytotoxic T-lymphocyte responses and antitumour immunity. *Immunology* **2007**, *120*, 90-102, 10.1111/j.1365-2567.2006.02483.x.

57. Angela Montecalvo; William J. Shufesky; Donna Beer Stolz; Mara G. Sullivan; Zhiliang Wang; Sherrie J. DiVito; Glenn D. Papworth; Simon C. Watkins; Paul D. Robbins; Adriana T. Larregina; et al. Exosomes As a Short-Range Mechanism to Spread Alloantigen between Dendritic Cells during T Cell Allorecognition. *The Journal of Immunology* **2008**, *180*, 3081-3090, 10.4049/jimmunol.180.5.3081.

58. Quan Liu; Darling M. Rojas-Canales; Sherrie J. DiVito; William J. Shufesky; Donna Beer Stolz; Geza Erdos; Mara L.G. Sullivan; Gregory A. Gibson; Simon C. Watkins; Adriana T. Larregina; et al. Donor dendritic cell–derived exosomes promote allograft-targeting immune response. *Journal of Clinical Investigation* **2016**, *126*, 2805-2820, 10.1172/jci84577.

59. Adrian E. Morelli; Adriana T. Larregina; William J. Shufesky; Mara L. G. Sullivan; Donna Beer Stolz; Glenn D. Papworth; Alan F. Zahorchak; Alison J. Logar; Zhiliang Wang; Simon C. Watkins; et al. Endocytosis, intracellular sorting, and processing of exosomes by dendritic cells. *Blood* **2004**, *104*, 3257-3266, 10.1182/blood-2004-03-0824.

60. Stefanie Hiltbrunner; Pia Larssen; Maria Eldh; Maria-Jose Martinez-Bravo; Arnika K. Wagner; Mikael C.I. Karlsson; Susanne Gabrielsson; Exosomal cancer immunotherapy is independent of MHC molecules on exosomes. *Oncotarget* **2016**, *7*, 38707-38717, 10.18632/oncotarget.9585.

61. Pia Larssen; Rosanne E. Veerman; Gözde Güçlüler Akpinar; Stefanie Hiltbrunner; Mikael C. I. Karlsson; Susanne Gabrielsson; Allogenicity Boosts Extracellular Vesicle–Induced Antigen-Specific Immunity and Mediates Tumor Protection and Long-Term Memory In Vivo. *The Journal of Immunology* **2019**, *203*, 825-834, 10.4049/jimmunol.1801628.

62. Khaleda Rahman Qazi; Ulf Gehrmann; Emilie Domange Jordö; Mikael C. I. Karlsson; Susanne Gabrielsson; Antigen-loaded exosomes alone induce Th1-type memory through a B cell–dependent mechanism. *Blood* **2009**, *113*, 2673-2683, 10.1182/blood-2008-04-153536.

63. Tanja I. Näslund; Ulf Gehrmann; Khaleda R. Qazi; Mikael C. I. Karlsson; Susanne Gabrielsson; Dendritic Cell–Derived Exosomes Need To Activate Both T and B Cells To Induce Antitumor Immunity. *The Journal of Immunology* **2013**, *190*, 2712-2719, 10.4049/jimmunol.1203082.

64. Robbie B. Mailliard; Shinichi Egawa; Quan Cai; Anna Kalinska; Svetlana N. Bykovskaya; Michael T. Lotze; Martien L. Kapsenberg; Walter J. Storkus; Paweł Kaliński; Complementary Dendritic Cell–activating Function of CD8+ and CD4+ T Cells. *Journal of Experimental Medicine* **2002**, *195*, 473-483, 10.1084/jem.20011662.

65. Roman Spörri; Caetano Reis E Sousa; Newly activated T cells promote maturation of bystander dendritic cells but not IL-12 production.. *The Journal of Immunology* **2003**, *171*, 6406-6413, 10.4049/jimmunol.171.12.6406.

66. Christiane Ruedl; Manfred Kopf; Martin F. Bachmann; CD8+ T Cells Mediate CD40-independent Maturation of Dendritic Cells In Vivo. *Journal of Experimental Medicine* **1999**, *189*, 1875-1884, 10.1084/jem.189.12.1875.

67. Marthe F. S. Lindenbergh; Daniëlle G. J. Koerhuis; Ellen G. F. Borg; Esther M. Van ‘T Veld; Tom A. P. Driedonks; Richard Wubbolts; Willem Stoorvogel; Marianne Boes; Bystander T-Cells Support Clonal T-Cell Activation by

Controlling the Release of Dendritic Cell-Derived Immune-Stimulatory Extracellular Vesicles. *Frontiers in Immunology* **2019**, *10*, 448, 10.3389/fimmu.2019.00448.

68. Julia Mallegol; Guillaume Van Niel; Corinne Lebreton; Yves Lepelletier; Céline Candalh; Christophe Dugave; Joan K. Heath; Graça Raposo; Nadine Cerf–Bensussan; Martine Heyman; et al. T84-Intestinal Epithelial Exosomes Bear MHC Class II/Peptide Complexes Potentiating Antigen Presentation by Dendritic Cells. *Gastroenterology* **2007**, *132*, 1866-1876, 10.1053/j.gastro.2007.02.043.

69. Fleur Aline; Daniel Bout; Sébastian Amigorena; Philippe Roingeard; Isabelle Dimier-Poisson; Toxoplasma gondii Antigen-Pulsed-Dendritic Cell-Derived Exosomes Induce a Protective Immune Response against T. gondii Infection. *Infection and Immunity* **2004**, *72*, 4127-4137, 10.1128/iai.72.7.4127-4137.2004.

70. Jesus Colino; Clifford M. Snapper; Exosomes from bone marrow dendritic cells pulsed with diphtheria toxoid preferentially induce type 1 antigen-specific IgG responses in naive recipients in the absence of free antigen.. *The Journal of Immunology* **2006**, *177*, 3757-3762, 10.4049/jimmunol.177.6.3757.

71. Stephan Munich; Andrea Sobo-Vujanovic; William J. Buchser; Donna Beer-Stolz; Nikola L. Vujanovic; Dendritic cell exosomes directly kill tumor cells and activate natural killer cells via TNF superfamily ligands. *OncoImmunology* **2012**, *1*, 1074-1083, 10.4161/onci.20897.

72. Venkateswara Rao Simhadri; Katrin S. Reiners; Hinrich P. Hansen; Daniela Topolar; Vijaya Lakshmi Simhadri; Klaus Nohroudi; Thomas A. Kufer; Andreas Engert; Elke Pogge Von Strandmann; Dendritic Cells Release HLA-B-Associated Transcript-3 Positive Exosomes to Regulate Natural Killer Function. *PLOS ONE* **2008**, *3*, e3377, 10.1371/journal.pone.0003377.

73. Cristina P.R. Xavier; Hugo R. Caires; Mélanie A. G. Barbosa; Rui Bergantim; José E. Guimarães; M. Helena Vasconcelos; The Role of Extracellular Vesicles in the Hallmarks of Cancer and Drug Resistance. *Cells* **2020**, *9*, 1141, 10.3390/cells9051141.

74. Fabrice Andre; Noel E C Schartz; Mojgan Movassagh; Caroline Flament; Patricia Pautier; Philippe Morice; Christophe Pomel; Catherine Lhomme; Bernard Escudier; Thierry Le Chevalier; et al. Malignant effusions and immunogenic tumour-derived exosomes. *The Lancet* **2002**, *360*, 295-305, 10.1016/s0140-6736(02)09552-1.

75. Carolina F. Ruivo; Bárbara Adem; Miguel Silva; Sónia A. Melo; The Biology of Cancer Exosomes: Insights and New Perspectives. *Cancer Research* **2017**, *77*, 6480-6488, 10.1158/0008-5472.can-17-0994.

76. Norahayu Othman; Rahman Jamal; Nadiah Abu; Cancer-Derived Exosomes as Effectors of Key Inflammation-Related Players. *Frontiers in Immunology* **2019**, *10*, 2103, 10.3389/fimmu.2019.02103.

77. Ihor Arkhypov; Samantha Lasser; Vera Petrova; Rebekka Weber; Christopher Groth; Jochen Utikal; Peter Altevogt; Viktor Umansky; Myeloid Cell Modulation by Tumor-Derived Extracellular Vesicles. *International Journal of Molecular Sciences* **2020**, *21*, 6319, 10.3390/ijms21176319.

78. Oleg Markov; Anastasiya Oshchepkova; Nadezhda Mironova; Immunotherapy Based on Dendritic Cell-Targeted/-Derived Extracellular Vesicles—A Novel Strategy for Enhancement of the Anti-tumor Immune Response. *Frontiers in Pharmacology* **2019**, *10*, 1152, 10.3389/fphar.2019.01152.

79. Jonathan M. Pitt; F. André; Sebastian Amigorena; Jean-Charles Soria; Alexander Eggermont; Guido Kroemer; Laurence Zitvogel; Dendritic cell–derived exosomes for cancer therapy. *Journal of Clinical Investigation* **2016**, *126*, 1224-1232, 10.1172/jci81137.

80. Aled Clayton; Jacquelyn Court; Hossein Navabi; Malcolm Adams; Malcolm D Mason; Jan A Hobot; Geoff R Newman; Bharat Jasani; Analysis of antigen presenting cell derived exosomes, based on immuno-magnetic isolation and flow cytometry. *Journal of Immunological Methods* **2001**, *247*, 163-174, 10.1016/s0022-1759(00)00321-5.

81. Clotilde Théry; Armelle Regnault; Jérôme Garin; Joseph Wolfers; Laurence Zitvogel; Paola Ricciardi-Castagnoli; Graça Raposo; Sebastian Amigorena; Molecular Characterization of Dendritic Cell-Derived Exosomes. *Journal of Cell Biology* **1999**, *147*, 599-610, 10.1083/jcb.147.3.599.

82. Yanfang Liu; Yan Gu; Xuetao Cao; The exosomes in tumor immunity. *OncoImmunology* **2015**, *4*, e1027472, 10.1080/2162402x.2015.1027472.

83. Akihiro Matsumoto; Maho Asuka; Yuki Takahashi; Yoshinobu Takakura; Antitumor immunity by small extracellular vesicles collected from activated dendritic cells through effective induction of cellular and humoral immune responses. *Biomaterials* **2020**, *252*, 120112, 10.1016/j.biomaterials.2020.120112.

84. Shisheng Chen; Mingfen Lv; Shan Fang; Wenxia Ye; Yu Gao; Yunsheng Xu; Poly(I:C) enhanced anti-cervical cancer immunities induced by dendritic cells-derived exosomes. *International Journal of Biological Macromolecules* **2018**, *113*, 1182-1187, 10.1016/j.ijbiomac.2018.02.034.

85. Martina Damo; David S. Wilson; Eleonora Simeoni; Jeffrey A. Hubbell; TLR-3 stimulation improves anti-tumor immunity elicited by dendritic cell exosome-based vaccines in a murine model of melanoma. *Scientific Reports* **2015**, *5*, 17622, 10.1038/srep17622.
86. Shasha Guan; Qianru Li; Pingping Liu; Xiaoyan Xuan; Ying Du; Experimental immunology Umbilical cord blood-derived dendritic cells loaded with BGC823 tumor antigens and DC-derived exosomes stimulate efficient cytotoxic T-lymphocyte responses and antitumor immunity in vitro and in vivo. *Central European Journal of Immunology* **2014**, *2*, 142-151, 10.5114/ceji.2014.43713.
87. Simona Anticoli; Francesco Manfredi; Chiara Chiozzini; Claudia Arenaccio; Eleonora Olivetta; Flavia Ferrantelli; Antonio Capocefalo; Emiliana Falcone; Anna Ruggieri; Maurizio Federico; et al. An Exosome-Based Vaccine Platform Imparts Cytotoxic T Lymphocyte Immunity Against Viral Antigens. *Biotechnology Journal* **2018**, *13*, e1700443, 10.1002/biot.201700443.
88. Zachary C. Hartman; Junping Wei; Oliver K. Glass; Hongtao Guo; Gangjun Lei; Xiao-Yi Yang; Takuya Osada; Amy Hobeika; Alain Delcayre; Jean-Bernard Le Pecq; et al. Increasing vaccine potency through exosome antigen targeting. *Vaccine* **2011**, *29*, 9361-9367, 10.1016/j.vaccine.2011.09.133.
89. Sophie Viaud; Magali Terme; Caroline Flament; Julien Taieb; Fabrice André; Sophie Novault; Bernard Escudier; Caroline Robert; Sophie Caillat-Zucman; Thomas Tursz; et al. Dendritic Cell-Derived Exosomes Promote Natural Killer Cell Activation and Proliferation: A Role for NKG2D Ligands and IL-15Rα. *PLoS ONE* **2009**, *4*, e4942, 10.1371/journal.pone.0004942.
90. Michael A Morse; Jennifer Garst; Takuya Osada; Shubi Khan; Amy C Hobeika; Timothy M Clay; Nancy Valente; Revati Shreeniwas; Mary Ann Sutton; Alain Delcayre; et al. A phase I study of dexosome immunotherapy in patients with advanced non-small cell lung cancer. *Journal of Translational Medicine* **2005**, *3*, 9-9, 10.1186/1479-5876-3-9.
91. Bernard Escudier; Thierry Dorval; Nathalie Chaput; F. André; Marie-Pierre Caby; Sophie Novault; Caroline Flament; Christophe Leboulaire; Christophe Borg; Sebastian Amigorena; et al. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of thefirst phase I clinical trial. *Journal of Translational Medicine* **2005**, *3*, 10-10, 10.1186/1479-5876-3-10.
92. Shengming Dai; Dong Wei; Zhen Wu; Xiangyang Zhou; Xiaomou Wei; Haixin Huang; Guisheng Li; Phase I Clinical Trial of Autologous Ascites-derived Exosomes Combined With GM-CSF for Colorectal Cancer. *Molecular Therapy* **2008**, *16*, 782-790, 10.1038/mt.2008.1.
93. Benjamin Besse; Mélinda Charrier; Valérie Lapierre; Eric Dansin; Olivier Lantz; David Planchard; Thierry Le Chevalier; Alain Livartoski; Fabrice Barlesik; Agnès Laplanche; et al. Dendritic cell-derived exosomes as maintenance immunotherapy after first line chemotherapy in NSCLC. *OncoImmunology* **2015**, *5*, e1071008-e1071008, 10.1080/2162402x.2015.1071008.
94. Alois Jungbauer; Exosomes Enter Vaccine Development: Strategies Meeting Global Challenges of Emerging Infections. *Biotechnology Journal* **2018**, *13*, e1700749, 10.1002/biot.201700749.
95. Seraphin Kuate; Jindrich Cinatl Jr.; Hans Wilhelm Doerr; Klaus Überla; Exosomal vaccines containing the S protein of the SARS coronavirus induce high levels of neutralizing antibodies. *Virology* **2007**, *362*, 26-37, 10.1016/j.virol.2006.12.011.
96. Carly M. Bliss; Andrea J. Parsons; Raffael Nachbagauer; Jennifer R. Hamilton; Federica Cappuccini; Marta Ulaszewska; Jason P. Webber; Aled Clayton; Adrian V. S. Hill; Lynda Coughlan; et al. Targeting Antigen to the Surface of EVs Improves the In Vivo Immunogenicity of Human and Non-human Adenoviral Vaccines in Mice. *Molecular Therapy - Methods & Clinical Development* **2020**, *16*, 108-125, 10.1016/j.omtm.2019.12.003.
97. Norbert Pardi; Michael J. Hogan; Frederick W. Porter; Drew Weissman; mRNA vaccines — a new era in vaccinology. *Nature Reviews Drug Discovery* **2018**, *17*, 261-279, 10.1038/nrd.2017.243.
98. Ugur Sahin; Evelyna Derhovanessian; Matthias Miller; Björn-Philipp Kloke; Petra Simon; Martin Löwer; Valesca Bukur; Arbel D. Tadmor; Ulrich Luxemburger; Barbara Schrörs; et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* **2017**, *547*, 222-226, 10.1038/nature23003.
99. Silvia Sánchez-Ramón; Laura Conejero; Mihai G. Netea; David Sancho; Óscar Palomares; José Luis Subiza; Trained Immunity-Based Vaccines: A New Paradigm for the Development of Broad-Spectrum Anti-infectious Formulations. *Frontiers in Immunology* **2018**, *9*, 2936, 10.3389/fimmu.2018.02936.