UNIVERSIDADE FEDERAL RURAL DE PERNAMBUCO - UFRPE

PROGRAMA DE PÓS-GRADUAÇÃO EM DESENVOLVIMENTO E INOVAÇÃO TECNOLÓGICA EM MEDICAMENTOS – PGDITM

USO DE MICROPARTÍCULAS POLIMÉRICAS COM ETOPOSÍDEO RADIOMARCADAS COM TECNÉCIO 99 METAESTÁVEL PARA O DIAGNÓSTICO DIFERENCIAL DE CÂNCER DE PULMÃO

Roberto Paulo Camara Salvi

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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-graduação em Desenvolvimento e Inovação Tecnológica em Medicamentos – PGDITM, da Universidade Federal Rural De Pernambuco.

Orientador: Prof. Dr. Ralph Santos-Oliveira

Co-Orientadora: Profa. Dra. Patrícia Lopes Barros de Araújo

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RESUMO

O diagnóstico de câncer de pulmão ocorre principalmente quando o câncer já está em estágio avançado. Nessa situação, há poucas opções para o tratamento e a maioria delas tem poucas chances de sucesso. Neste estudo foram desenvolvidas e testadas micropartículas de Etoposídeo como um agente de diagnóstico para imagem de câncer pulmonar em estágios iniciais de desenvolvimento. Micropartículas de Etoposídeo marcadas com tecnécio 99 metaestável foram testadas em ratos induzidos. Os resultados demonstraram que mais de 10% da dose total utilizada foi de absorvida no local do tumor. Além disso, os resultados mostraram que as micropartículas tinham uma boa depuração renal e absorção pelo fígado e baço. Os dados sugerem que estes micro-radiofármacos podem ser utilizados para exame de imagem do câncer de pulmão, especialmente tomografia computadorizada por emissão de fóton único (SPECT).

Palavras-chave: Nanopartícula, Citotoxicidade, Etoposídeo, Nanopartículas Poliméricas, Tecnécio-99m.

ABSTRACT

The diagnosis of lung cancer mostly occurs when the cancer is already in an advanced stage. In this situation, there are few options for the treatment and most of them have few chances of success. In this study, we developed and tested etoposide microparticles as a diagnostic agent for imaging lung cancer at early stages of development. We tested etoposide microparticles labeled with technetium 99m in inducted mice. The results demonstrated that over 10% of the total dose used was uptake by the tumor site. Also, the results showed that the microparticles had a good renal clearance and low uptake by liver and spleen. The data suggest that these micro-radiopharmaceuticals may be used for lung cancer imaging exam, especially single-photo emission computed tomography (SPECT).

Keywords: Nanoparticle, Cytotoxicity, Etoposide, Polymer Nanoparticles, Technetium-99m.

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LISTA DE ABREVIATURAS E SIGLAS

ANVISA	Agência Nacional de Vigilância Sanitária - National Health Surveillance Agency
EPR	Efeito Permeabilidade e Retenção Aumentadas - Enhanced Permeability and Retention
NP’s	Nanopartículas – Nanoparticles
MP`s	Micropartículas - Microparticles
PET	Tomografia por Emissão de Positron - Positron Emission Tomography
PCL	Policaprolactona - Polycaprolactone
PLA	Ácido Poliláctico - Polylactic Acid
PLGA	Poli (Ácido Láctico-co- Ácido glicólico) - Poly (Lactic acid-co-glycolic acid)
SPECT	Tomografia Computadorizada por Emissão de Fóton Único - Single-Photon Emission Computed Tomography
TC	Tomografia Computadorizada - Computed Tomography
α	Alfa
β	Beta
ɣ	Gama

SUMÁRIO

INTRODUÇÃO

O câncer é definido como um conjunto de doenças (>100 tipos), caracterizado por um crescimento desordenado e anormal de células que se tornam capazes de invadir os mais variados tecidos e órgãos (INCA, 2018a). Nas últimas décadas o câncer, se tornou uma epidemia de proporções globais, em especial nos países desenvolvidos, com uma prospecção de aproximadamente 18,1 milhões de novos casos de câncer, com 9,6 milhões de morte em 2018 (BRAY et al., 2018a).

Dentre os diversos tipos de câncer, o de pulmão é o segundo mais incidente, com mais de 2,1 milhões de novos casos de câncer de pulmão por ano em todo o mundo (BRAY et al., 2018b). No Brasil, foram registrados 31.270 novos casos em 2018, e atinge tanto homens como mulheres (DEVANATHAN; KIMBLE-HILL, 2018; MAHASE et al., 2018; WU et al., 2018a). O câncer de pulmão ocupa a posição de primeiro no ranking, quando considerados a incidência e mortalidade, representando 11,6% todos os novos casos de câncer no mundo (HSIN; HO, 2018; RICH; BECKETT; BALDWIN, 2018; WU et al., 2018a).

O câncer de pulmão pode ser definido como uma patologia que acomete vias aéreas e/ou parênquima pulmonar (GEMINE et al., 2019; HSIN; HO, 2018; RICH; BECKETT; BALDWIN, 2018; WU et al., 2018a). Não obstante, a classificação histológica o divide em 4 tipos: carcinoma de pequenas células, carcinoma escamoso ou epidermóide, adenocarcinoma e carcinoma de células não pequenas (GEMINE et al., 2019; SATO, 2018). Contudo, de forma clínica ele é dividido em 2 grandes tipos: carcinoma de células não pequenas e carcinoma de células pequenas (AI et al., 2018; MASON et al., 2017). Estas classificações são baseadas nas diferenças clinicas, poder metastático e resposta terapêutica (BATUM et al., [s.d.]; BREITBACH et al., 2018; JUNGRAITHMAYR, 2018; WINK et al., 2019).

O principal fator de risco associado ao câncer de pulmão é o tabagismo, seja ele ativo ou passivo. Desde a década de 50, estudos apontam o tabagismo como uma das principais causas do desenvolvimento da doença (CASTELLETTI et al., 2019; WU et al., 2018b; ZHENG; CHEN, 2018). O quadro clínico inicial do câncer de pulmão, não possui sintomatologia específica e, pode manifestar-se por meio de sintomas comuns, tais como:

dispnéia, tosse, hemoptise e perda de peso. Em apenas 15% dos casos, o diagnóstico, é feito de forma precoce, levando ao incremento da sobrevida do paciente (HOUGHTON, 2018; SOLASS et al., 2016; XIONG; WANG; YU, 2018)

O diagnóstico é realizado por meio de exames de imagens inespecíficos como Raios-X e Tomografia Computadorizada (TC). Posteriormente podem ser necessários exames complementares, como uma endoscopia respiratória (broncoscopia) com a coleta de material para biópsia para complementação de diagnóstico (GORHAM et al., 2019; KHADEM ANSARI et al., 2018; LEE, 2018a; POMPILI et al., 2018; PROTO et al., 2019)

1. Revisão Bibliográfica

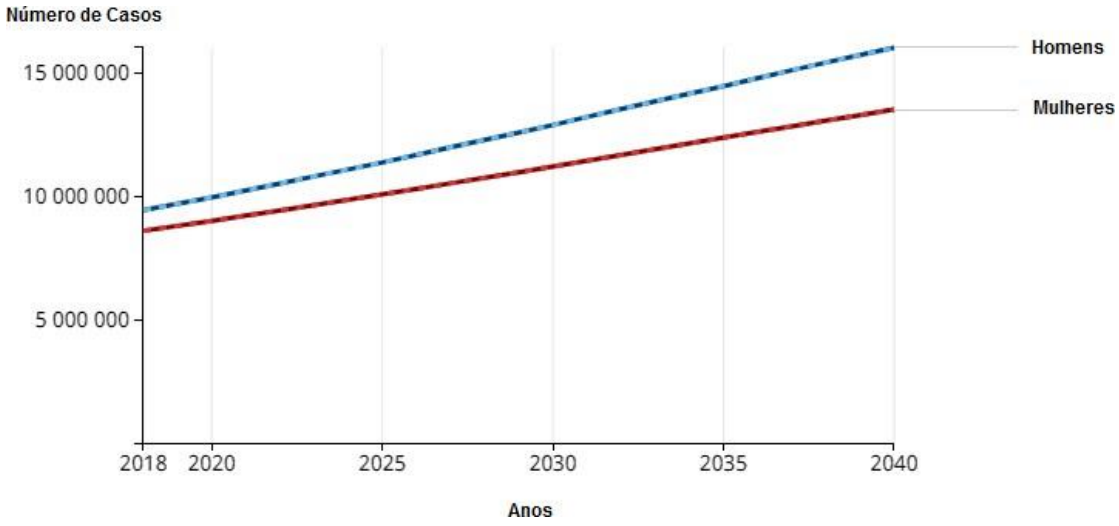
1.1.Câncer

O câncer é uma patologia caracterizada pelo crescimento anormal de células que são capazes de invadir tecidos e órgãos e podem espalhar-se para outras regiões do corpo (GHONCHEH; POURNAMDAR; SALEHINIYA, 2016; INCA, 2018b). A metástase pode ocasionar a presença de tumores em regiões de difícil acesso ao tratamento, aumentando a comorbidade associada à doença (SIMSEK; BASOL TEKIN; BILICI, 2019; SOLASS et al., 2016). Sua ocorrência é multifatorial (ambiental, genética entre outras) ocasionando mudanças sucessivas na sobrevida celular, em especial levando a alterações no processo de multiplicação, diferenciação e interação celular (GAO et al., 2018; KRÓLCZYK et al., 2018; ONICESCU et al., 2018).

Os tipos de câncer estão relacionados aos tecidos do organismo onde se desenvolvem inicialmente, o câncer que se desenvolve em tecidos epiteliais, tais como: pele ou mucosa, é conhecido como carcinoma (BATTELLI et al., 2019; KOTCHERLAKOTA; RAHAMAN; PATRA, 2019; ZHAO et al., 2019). Já o câncer que se desenvolve em tecidos conjuntivos, tais como: osso, musculo ou cartilagem, é conhecido como sarcoma. (DALGLEISH; STERN, 2018; KURUBA; GOLLAPALLI, 2018; MATUSZEWSKI et al., 2018; WANG et al., 2019a; XU et al., 2018).

No ano de 2018, são previstos, no Brasil, aproximadamente, 576 mil novos casos de câncer de pulmão (Gráfico 1) (SILVER et al., 2018; STANKOVIC et al., 2019a). O câncer é uma patologia assintomática, entretanto, alguns sintomas podem ser notados dependendo da região em que o tumor esteja se desenvolvendo, dentre alguns fatores que podemos citar: fadiga crônica, perda de peso, dor, febre, mudanças na pele estão entre esses fatores. (UEDA et al., 2019; XIAO et al., 2018).

Gráfico 1 - Número estimado de casos incidentes de 2018 a 2040, todos os cânceres, homens e mulheres, todas as idades.



Fonte: GLOBOCAN, 2018

1.2. Carcinogênese

A carcinogênese é o processo de formação do câncer. Este processo ocorre lentamente podendo levar anos até que seja possível visualiza-lo na forma de tumor. De modo geral, o crescimento celular possui um controle complexo e dependente de expressão gênica (BERRY, 2018; CLEMENTINO; SHI; ZHANG, 2018; COZAR et al., 2018). Os processos de crescimento e diferenciação celular são controlados pelos protooncogenes, estes por sua vez também são responsáveis pelo controle da divisão mitótica (BINATO et al., 2018; LALLEMAND et al., 2018).

Por meio de ativações anormais dos genes ou mutações gênicas, os protooncogenes são transformados em oncogênese. Estes por sua vez, tendem a aumentar a produção de proteínas para estimulação da divisão, inibição da diferenciação e da morte celular, desta forma, dão origem as células cancerosas, que se multiplicam de modo superior e procuram a eternidade (MA et al., 2017; MAZONAKIS et al., 2017).

A carcinogênese pode ser dividida em quatro estágios : início, promoção, conversão maligna e progressão tumoral. (LIU; SANIN; WANG, 2017; SAK, 2017; ZHANG et al., 2017). (Figura 1 e 2) (CALADO et al., [s.d.]; XU et al., 2019a).

O primeiro estágio é caracterizado por um período em que ocorrem modificações irreversíveis (LEDFORD, 2017; MENG et al., 2017). Essas modificações podem ser causadas por agentes externos e/ou internos que ocasionam modificações estruturais durante a síntese de DNA, acarretando mutações, resultando em modificação gênicas, e a formação de clones celulares anômalos (HUSSAIN et al., 2019; LIU et al., 2019a).

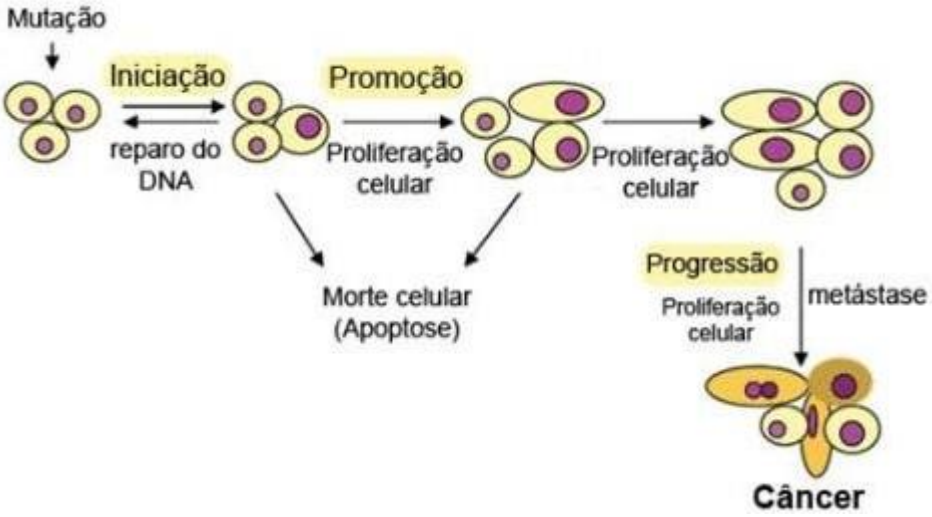
O segundo estágio, a promoção, é o momento onde ocorre a expansão dos clones das células modificadas/danificadas, no entanto, até este momento as células não apresentam caráter oncológico. Para tal necessitam de um ativador metabólico, que irá ser responsável para a conversão maligna. (MATSUI et al., 2017; RAHMAN et al., 2017; SCHMIDT et al., 2018).

No terceiro estágio as células podem ser convertidas e passar a expressar o fenótipo maligno. Uma fração destas células poderão sofrer divisões em tumores benignos ou lesões pré-neoplásicas, alguns fatores externos, como a alimentação e a exposição excessiva a hormônios, por exemplo, são fatores que influenciam a transformações de células em malignas (XU et al., 2019b; ZHANG; ZHANG, 2018).

O quarto estágio, a progressão, caracteriza-se pela propensão de células malignas em adquirir características agressivas ao longo do tempo, assim como a capacidade de metastatizar, associada a capacidade das células tumorais em excretar proteases que invadem outros lugares distantes do tumor primário e desta forma instalam-se e evoluem até as primeiras manifestações clínicas da doença (CAO, 2017; MOMMERSTEEG et al., 2018; TAO et al., 2019).

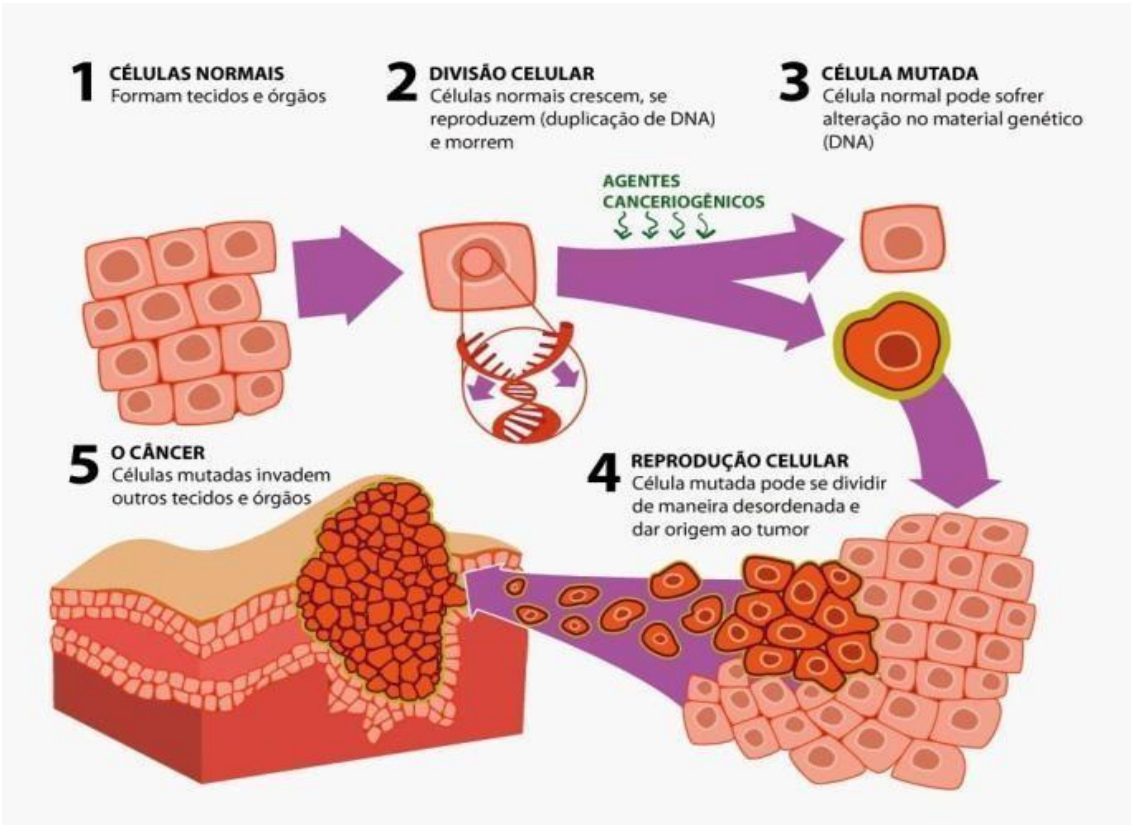
O processo de multiplicação desordenada de células forma novos vasos sanguíneos (angiogênese) que são responsáveis pelo abastecimento de nutrientes de forma adequada para as células cancerígenas. Estes vasos podem se desprender destes tumores e invadir tecidos adjacentes, posteriormente podem atingir a circulação sanguínea e desta forma atingir órgãos e assim, ajudar no processo de metástase também (MILLER; CONOLLY; KIMBELL, 2017; PIOTROWSKI et al., 2017; XU et al., 2017).

Figura 1- Etapas da formação de tumores



Fonte: Inca – Instituto Nacional de Câncer – Ministério da Saúde, 2016

Figura 2 - Esquema da formação de tumores



Fonte: Hospital Hélio Angotti, 2017

1.3. Câncer de Pulmão

O câncer de pulmão representa um dos tipos de câncer com maior incidência e mortalidade associada em todo o mundo. É o segundo mais comum para ambos os sexos e representa mais de 13% de todos os novos casos de câncer (EGE AKTAS; SARIKAYA; SOYLUOGLU DEMIR, 2017; JUNG et al., 2018). Durante a última estimativa mundial realizada em 2012, foram apontados 583 mil novos casos em mulheres e 1,24 milhões de novos casos em homens. No Brasil mais de 26 mil pessoas morreram em 2015 devido ao câncer de pulmão (Gráfico 2) (GAO et al., 2018; GUO; ZHENG, 2019). O tabagismo, bem como a exposição passiva aos derivados de tabaco são fatores de risco associados ao desenvolvimento de câncer de pulmão, em 85% dos casos. (Figura 3) (HAIDER et al., 2019; VAINSHELBOIM et al., 2019).

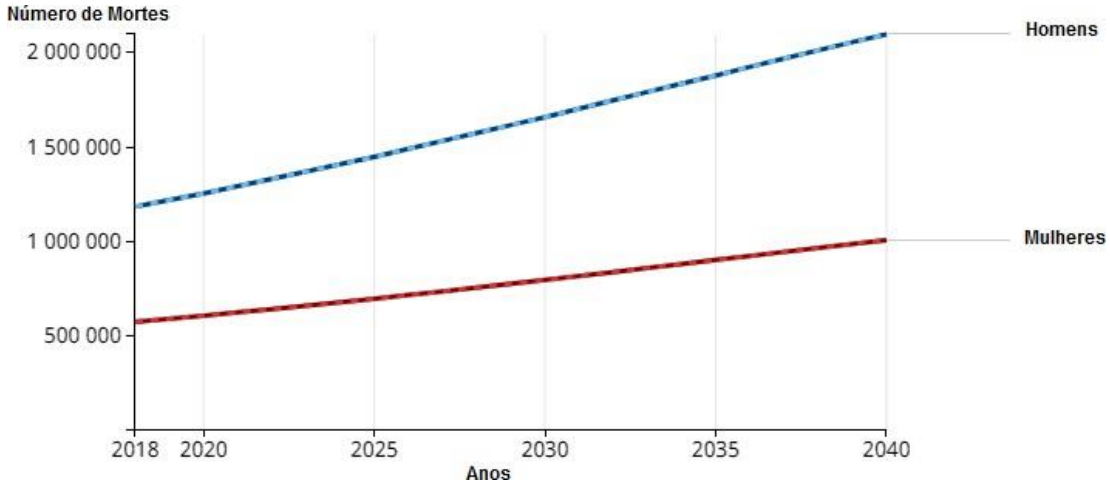
Em 90% dos casos, o câncer de pulmão é diagnosticado depois dos 50 anos, na faixa que compreende dos 60 aos 70 anos. Nas últimas décadas acreditava-se que o câncer de pulmão era uma patologia exclusiva do sexo masculino, contudo, dados recentes, apontam que isso era um mito, e os números de caso no sexo feminino vem aumentando progressivamente (KAPLAN, 2017; SAPPINGTON et al., 2018). Tal fato está associado a um maior consumo de tabaco e a uma maior dificuldade que mulheres apresentam em deixar de fumar. Não obstante, estudos comprovaram a maior susceptibilidade das mulheres aos efeitos cancerígenos dos componentes dos cigarros (ILIE et al., 2018; MAO et al., 2018; TAN et al., 2017).

O câncer de pulmão é caracterizado pelo surgimento de tumores nas células pulmonares. O mecanismo natural de multiplicação celular sofre alterações que levam ao crescimento desordenado de células mutantes com alto grau de malignidade nos pulmões (CARRERAS; GORINI, 2017; KURISHIMA et al., 2017; OBEID; PIETRZIK, 2018). O surgimento de tumores em decorrência desta mutação pode ocorrer não somente nos pulmões, como podem estar associados ao trato respiratório (FENG et al., 2017; NOMORI et al., 2018; VERGHESE; REDKO; FINK, 2018).

A identificação do tipo de câncer é feita através de análise de amostra das lesões. A partir disso, o câncer de pulmão pode ser divido como: câncer de pulmão de células não pequenas (CPNCP) e câncer de pulmão de células pequenas (CPPC). Além dessa divisão, o câncer de pulmão de células não pequenas é subdividido em três

subtipos: Adenocarcinoma (inclui o bronquíolo-alveolar, subtipo mais raro), Carcinoma de células escamosas e Carcinoma de células grandes (AKBARI SARI et al., 2017; BERTAGLIA et al., 2017; NAKAMURA; SANAI; MIWA, 2018; SHARMA; GOEL; LAL, [s.d.]).

Gráfico 2 - Número estimado de mortes por câncer de pulmão de 2018 a 2040, masculino e feminino, todas as idades.



Fonte: GLOBOCAN, 2018

Figura 3 - Números do câncer de Pulmão no Brasil e no Mundo.

Fonte: Adaptação de Global Lung Cancer Coalition, 2018

1.3.1. Câncer de Pulmão de Células Não Pequenas (CPCNP)

O câncer de pulmão de células não pequenas, também chamado de câncer de pulmão indiferenciado, apresenta um crescimento mais lento quando comparado a outros tipos de câncer, entretanto, sua capacidade em metastatizar é muito maior (DYER; DALY, 2017; HARDESTY; KANAREK, 2018; MAMDANI; JALAL, 2017; WOODFORD et al., 2017). De maneira geral, este tipo de câncer representa 80% dos casos de câncer de pulmão, podendo acometer qualquer parte do tecido pulmonar e na maioria das vezes se manifesta como nódulos ou massas periféricas,

podendo, também, acometer a a região pleural (IN et al., 2017; JACKY; BAIK, [s.d.]; ZHANG; YU; SHEN, 2018). Devido ao tipo de tecido e o local de crescimento do câncer pulmonar, ele pode ser dividido em dois tipos:

Tabela 1- Estágios do Câncer de Pulmão de Células Não Pequenas.

Estágio do Câncer de Pulmão de Células Não Pequenas	
Estágio 1A	O câncer é apenas nos pulmões, não está em nenhum dos gânglios linfáticos e tem menos de 3cm de diâmetro.
Estágio 1B	O câncer é apenas nos pulmões, não está em nenhum dos gânglios linfáticos, porém, pode ser: • O câncer é maior que 3cm. • O câncer está crescendo na via aérea principal do pulmão ou no revestimento interno do pulmão.
Etapa 2A	O câncer tem menos de 3cm, mas se espalhou para os nódulos linfáticos mais próximos do pulmão afetado.
Estágio 2B	• O câncer é maior que 3cm e há câncer nos gânglios linfáticos mais próximos do pulmão afetado. • O câncer cresceu para outras áreas próximas ao pulmão afetado, como a parede torácica.
Estágio 3A	• O câncer se espalhou para os gânglios linfáticos mais longe do pulmão afetado, mas ainda do mesmo lado do tórax. • Há câncer apenas nos gânglios linfáticos mais próximos do pulmão afetado, mas o câncer se espalhou para a parede torácica ou para o meio do peito.
Estágio 3B	• O câncer se espalhou para os gânglios linfáticos do outro lado do tórax ou para os nódulos acima da clavícula. • Há mais de um tumor no pulmão. • O tumor cresceu em outra parte principal do seu peito. • Há fluido em torno de seus pulmões que contém células cancerígenas.
Estágio 4	O câncer se espalhou para outra parte do corpo, por exemplo, fígado ou ossos.

Fonte: Adaptação de Global Lung Cancer Coalition, 2018

1.3.1.1.Adenocarcinoma Pulmonar

Este tipo de tumor acomete, principalmente, ex-fumantes e é o tipo mais comum em pessoas não fumantes. A maior incidência deste tipo de câncer está associada a mulheres jovens (JOUINOT et al., 2018; YAMASAKI et al., 2018; YANG et al., 2018b). O adenocarcinoma pulmonar é frequentemente encontrado nas áreas externas do pulmão, possui um crescimento lento, tornando possível seu diagnostico antes da metástase. Os tumores se iniciam em células de revestimento alveolar responsáveis pela produção de muco (LEE,

2018b; LIM et al., 2018a; LIU et al., 2019b; STANKOVIC et al., 2019b).

1.3.1.2. Carcinoma Escamoso ou Epidermóide

Este tipo de câncer está frequentemente associado a fumantes, geralmente acomete pessoas idosas com histórico de tabagismos por longos períodos (LI et al., [s.d.]; OGHALAIE et al., 2017). É caracterizado pelo crescimento irregular de células do revestimento do interior das vias aéreas na região central dos pulmões próximo aos brônquios (AIRES et al., 2017; WANG et al., 2017). O crescimento deste tumor pode levar a um bloqueio na passagem de ar nos pulmões levando a dificuldade de respiração. Este tipo de tumor, em grande parte dos casos, pode ser removido através de cirurgias (MAHFOUD et al., 2017; WANG; YANG; ZHUANG, 2017; YU et al., 2017).

1.3.2. Câncer de Pulmão de Pequenas Células (CPPC)

Este tipo de câncer representa aproximadamente 20% dos casos de câncer de pulmão e atinge ambos os sexos, além disso, está associado ao tabagismo ao longo da vida (DEAN; SUBEDI; LEE, 2018a; GLATZER et al., 2017; ZHANG; SUN; JIANG, 2018a). De forma geral, o CPPC tem seu início nos brônquios, localizado na região central do pulmão e vias aéreas, sendo considerado a forma mais agressiva de câncer de pulmão (DEAN; SUBEDI; LEE, 2018b; ZHANG; SUN; JIANG, 2018b). A metástase ocorre de forma rápida e progressiva. Em termos gerais, 60% dos pacientes diagnosticados com CPPC apresenta a doença em estágios avançados e com metástase (FRENZEL et al., 2018a, 2018b; PETRUSEVSKA et al., 2017; XIONG et al., 2018).

Tabela 2 - Estágios do Câncer de Pulmão de Pequenas Células

Estágio do Câncer de Pulmão de Pequenas Células	
Estágio limitado →	O câncer é apenas em um pulmão
Estágio extensivo →	O câncer se espalhou para outras partes do corpo

Fonte: Adaptação de Global Lung Cancer Coalition, 2018

1.3.3. Outros Tipos de Câncer de Pulmão

1.3.3.1. Mesotelioma

Este é o tipo de câncer pulmonar associado a um histórico de exposição a amianto, geralmente associado a trabalhadores diretamente ligados a indústria de produção de produtos que contenham amianto (BLYTH; MURPHY, 2018; SADDOUGHI; ABDELSATTAR; BLACKMON, 2018). Frequentemente, este câncer afeta principalmente homens na faixa dos 35- 40 anos. (MORIYAMA et al., 2017; TRANCHANT et al., 2018; YIN et al., 2017).

O Mesotelioma se desenvolve nos revestimentos pulmonares e aumenta a capacidade de produção de fluidos, no entanto, esses fluidos não são facilmente expelidos e necessitam de drenagens frequentes para a melhora da respiração do paciente (CROVELLA et al., 2018; QIN et al., 2017; TSAO et al., 2018; XING et al., 2018).

1.3.3.2. Tumor Carcinoide

No geral, esse câncer representa de 1 a 2% dos casos de câncer de pulmão. Os tumores têm início nas vias respiratórias menores e nas periferias dos pulmões (CHU; EL-ANNAN, 2018; KIDD et al., 2018; OUEDE et al., 2017). Esse tipo de tumor pode causar bloqueio parcial ou total da passagem de ar e possui sintomas muito parecidos com pneumonia, este fato é o principal responsável pelo diagnostico tardio, uma vez que os médicos só conseguem diagnostica-lo após o uso de antibióticos onde observam a permanência dos sintomas

(ALJASSEM; ALJASEM, 2018; MOHAPATRA et al., 2017; OLOFSON; TAFE, 2018; VAHIDI et al., 2018).

Estes tumores são assintomáticos nos estágios inicias, porém, em estágios avançados interferem na respiração e seu diagnóstico é realizado por radiografia ou tomografia onde podem ser observados pontos (CUSUMANO et al., 2017).

1.4. Diagnóstico

De maneira geral, o diagnóstico do câncer de pulmão é crucial para o aumento da sobrevida do paciente. O diagnóstico, na sua maioria é proveniente de análises tomográfica de tórax ou radiografia de tórax, em casos mais avançados, é necessária uma biópsia do tumor para garantia de identificação do tipo de tumor em questão (CHATURVEDI et al., 2018; SNOECKX et al., 2019). A escolha do procedimento ideal para a identificação do tumor vai depender da localização da massa a ser investigada. Quando em regiões mais centrais do pulmão, é recomendado a Broncoscopia (Figura 4) (BRUN et al., 2018; QIN; DUA, 2017). Tumores localizados em regiões periféricas do pulmão, região de surgimento do adenocarcinoma, são recomendados procedimentos mais eficientes como a biópsia guiada por tomografia (Figura 5) (LIM et al., 2018b; SNOECKX et al., 2017; WINK et al., 2019; WOLF et al., 2019).

Em alguns casos, os pacientes podem apresentar os linfonodos aumentados em regiões pulmonares próximas ao tumor ou na região central do tórax, chamada de mediastino. Nestes casos, onde há suspeita de invasão dos linfonodos, é indicado a retirada por cirurgia para uma correta avaliação, este procedimento é denominado mediastinoscopia (BOUGIOUKAS; SEIPELT; HUWER, 2019; SPEAR et al., 2019). Em determinados centros especializados, a biópsia do mediastino também pode ser realizada por ultrassom endoscópico através do esôfago ou até mesmo através dos brônquios grandes localizados no mediastino (EGBERTS et al., 2019; OĞUZ KAPICIBAŞI, 2019; SANTOS SILVA; COSTA; CALVINHO, 2019).

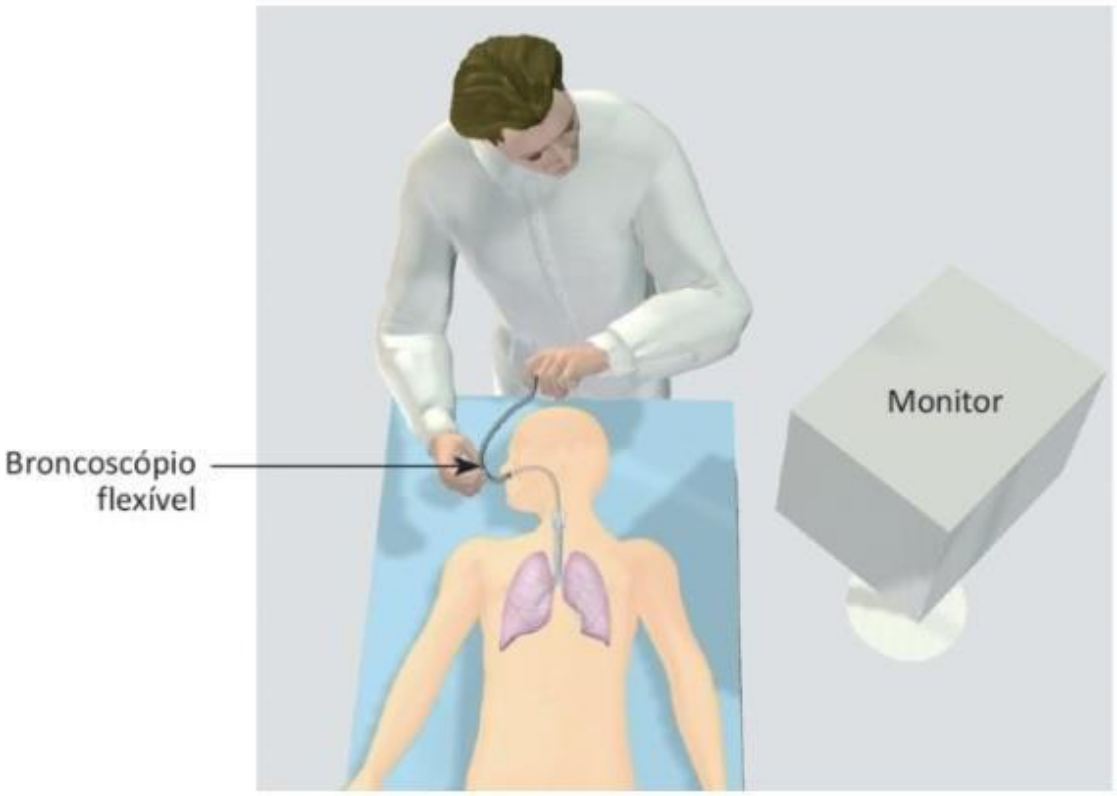
1.4.1. Tomografia computadorizada por emissão de fóton único (SPECT)

A tomografia computadorizada por emissão de fóton único, também concedida como SPECT, foi desenvolvida nas décadas de 1960 e 1970 para ser amplamente disponível como uma opção de diagnóstico por imagem (D'ARIENZO; COX, 2017; GOLDKLANG et al., 2019). O sistema consiste em uma gama câmara com três detectores de NaI (Iodeto de Sódio), computador que permite a aquisição e processamento de dados e um sistema especifico para exibição (DURMO et al., 2019; NUDI et al., 2019).

Para permitir a detecção do sistema SPECT, é utilizado radioisótopos que emitem radiação gama, tais como, ^{99m}Tc, ^{123}I, , ^{111}In e ^{67}Ga, na forma de radiofármacos: ^{99m}Tc-MAA, ^{99m}Tc-MIBI, ^{99m}Tc-ECD, entre outros. A radiação emitida por estes radioisótopos pode ser detectada pelo aparelho e processada em imagem (ABDOLLAHI et al., 2016; PRICE et al., 2019; SONG et al., 2019).

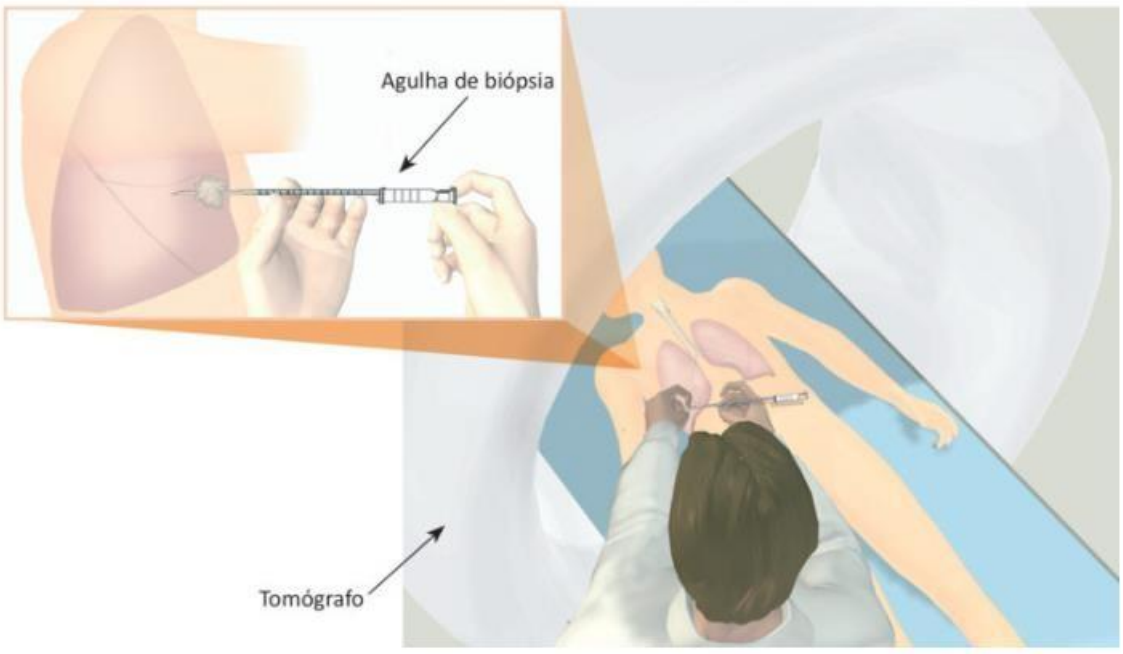
A sensibilidade da técnica de SPECT é muito alta, cerca de 95%, entretanto, a resolução anatômica é consideravelmente baixa, ficando próxima de 10 mm (HUTTON, 2014; KHALIL et al., 2011). Nestes casos, para uma localização mais precisa as imagens SPECT são necessariamente associadas a imagens de Tomografia Computadorizada e/ou Ressonância Magnética, visando oferecer uma avaliação mais eficaz (POLYAK; ROSS, 2018; SONG et al., 2017; YANG et al., 2018a).

Figure 4 - Realização do procedimento de Broncoscopia



Fonte: Instituto Vencer o Câncer, 2016

Figura 5 – Realização do Procedimento de Broncoscopia Guiado por Tomografia



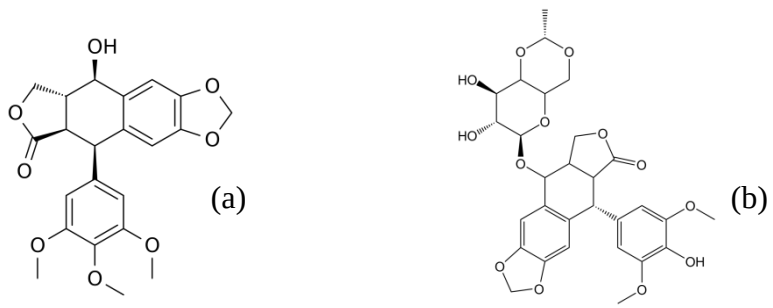
Fonte: Instituto Vencer o Câncer, 2016

1.5. Etoposídeo

O fosfato de Etoposídeo é um medicamento utilizado com a finalidade de retardar o crescimento de tumores variados. Este medicamento é um derivado semissintético da podofilotoxina, substância tóxica pertencente à classe das lignanas (PATEL et al., 2016; SAMBASIVAN et al., 2014). Esta substância é extraída do vegetal conhecido como Mandrágora Americana (Podophyllum Peltatum L.) que exibe atividade antitumoral (CAI et al., 2019; SAROJ; RAJPUT, 2018). A baixa toxicidade do Etoposídeo, quando comparado a podofilotoxina, é devido a mudanças conformacionais na estrutura da molécula, assim como a inserção de uma unidade de glicose a estrutura da podofilotoxina. (Figura 6)(BOYÉ et al., 2017; CORDERO et al., 2017; POLISTENA et al., 2017) .

A utilização desse medicamento no tratamento de câncer se deve a sua capacidade inibitória dos processos de multiplicação celular, mais especificamente, a inibição da topoisomerase II (LEGUAY et al., 2016; PEREZ-SOMARRIBA et al., 2019; WANG et al., 2019b; ZHANG et al., 2019a). Desta maneira, as células tumorais são impedidas de crescer, uma vez que seus processos de divisão são parados. O Etoposídeo atua na fase G2 do ciclo celular, através de indução à ruptura na alça dupla do DNA devido a sua interação enzimática com a DNA-topoisomerase II, assim o ciclo celular não pode ser concluído (FARNAULT et al., 2019; INABA et al., 2017; LAMARCA et al., 2018; SRINIVAS et al., 2015).

Figura 6- Estrutura Química da Podofilotoxina (a) comparado a estrutura do Etoposídeo (b)



Fonte: Autor

1.6. Radiofármacos

De acordo com definições da ANVISA, os radiofármacos são preparações farmacêuticas cuja a finalidade é diagnóstica ou terapêutica e que, quando prontas para o uso, devem conter um ou mais radionuclídeos (CAROLLO et al., 2019; KUNOS; CAPALA; IVY, 2019). Podem compreender componentes não-radioativos para marcação e os radionuclídeos, incluindo os componentes extraídos dos geradores de radionuclídeos (ANVISA, 2009). Para que um radionuclídeo seja ideal para uso ele deve possuir facilidade em ser produzido e meia vida física e biológicas suficientes para serem utilizadas nos procedimentos ao qual se destinam (AL-HADDAD; ISMAILANI; ROTSTEIN, 2019; BRANDT et al., 2019; KUNOS et al., 2019)

Cerca de 95% dos radiofármacos são utilizados para o diagnóstico, enquanto a porcentagem restante é utilizada com finalidade terapêutica (FAY; HOLLAND, 2019). Devido a sua principal fonte de administração ser a via intravenosa, devem apresentar grau de esterilidade, ser isentos de pirogênios e passar por todos os testes de controle de qualidade utilizados para medicamentos estéreis (KUNOS et al., 2019; MANTEL; WILLIAMS, 2019; OMAR et al., 2019)

Os medicamentos caracterizados como radiofármacos apresentam dois componentes: um radionuclídeo emissor de radiação de interesse, podendo ser α (alfa), β (beta) ou γ (gama), alguns radionuclídeos podem emitir mais de um tipo de radiação e por este motivo apresentam atividade teranóstico (terapia + diagnóstico) e um carreador que possua afinidade com o sítio alvo (DE SILVA et al., 2019; SCHMEISER et al., 2019; USMANI et al., 2019). Os radionuclídeos utilizados para diagnósticos, são geralmente, os emissores de raios gamas e pósitrons, uma vez que ambas as radiações atravessam o tecido com facilidade e são facilmente detectados por SPECT e PET, respectivamente. Cerca de 80% dos exames em medicina nuclear com finalidade diagnóstica utilizam o tecnécio 99 metaestável (^{99m}Tc) (KHAN et al., 2019; YANG et al., 2019a).

O tecnécio-99m apresenta uma meia física vida de 6,01 horas, é um radionuclídeo filho do Molibidênio-99, cuja meia vida física é de 66,02 horas (Figura 7). O decaimento radioativo dessa forma, possibilitou o desenvolvimento de geradores baseados em eluições que permitem a produção de radiofármacos de

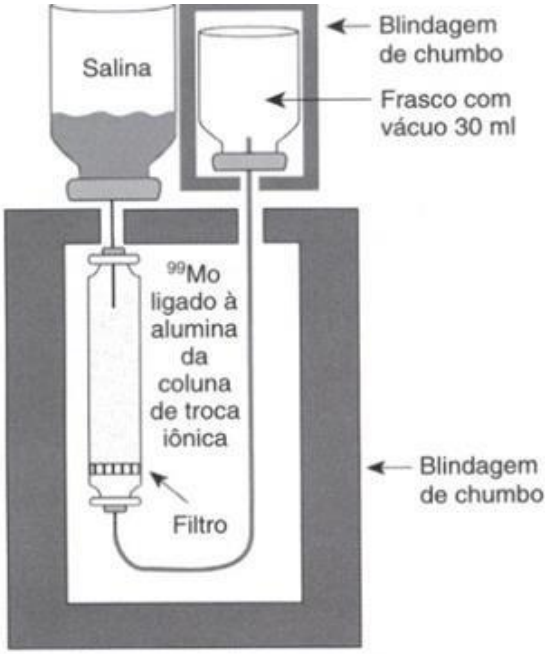
forma diária em radiofármacias dos serviços de medicina nuclear (DING et al., 2019a; JIANG; HOU; CHENG, 2019).

Os radiofármacos utilizados para terapia se baseiam em propriedades específicas dos radioisótopos chamadas de LET (linear Energy transfer, ou em português, transferência linear de energia). Desta maneira, os radioisótopos liberam quantidades de energias ionizantes que se depositam sobre a matéria causando a sua destruição, neste caso, da massa tumoral (SHARMA et al., 2019; SMALL; RUDDY, 2019a). Seguindo o conceito de Bergonie e Tribondeau, a sensibilidade que as células apresentam à radiação, é diretamente proporcional a sua capacidade de reprodução e inversamente proporcional ao seu grau de especialização (BRASSE; NONAT, 2015; MCCREADY, 2017).

Atualmente acredita-se que o futuro da radiofarmácia e da medicina nuclear se baseiam no uso de radionuclídeos na forma de nanopartículas (nanorradiofármacos) (ANTUGANOV et al., 2019; DING et al., 2019b; SMALL; RUDDY, 2019b). Está modalidade permite o uso de moléculas, tais como: anticorpos, peptídeos e siRNA. Estas biomoléculas possuem afinidade pelo organismo ao qual se deseja tratar pois, em sua grande maioria, são sintetizados tendo como base uma molécula do próprio organismo (YADAV; DHAGAT; ESWARI, 2019). Por esse motivo se mostram com excelente carreadores devido as suas características e similaridade que permitem um direcionamento da radiação ao tumor e possibilitando um uso mais eficaz (KLAUNIG, 2019; WANG et al., 2019c; ZHOU et al., 2019).

Para a produção do ^{99m}Tc, os serviços de medicina nuclear fazem uso do gerador de molibdênio -99/tecnécio-99 metaestável (^{99}Mo/^{99m}Tc) . O ^{99}Mo é produzido em um reator nuclear através da ativação do molibdênio natural enriquecido (^{98} Mo) com nêutrons ou através da fissão do ^{235}U. Após o processo de purificação química, ^{99}Mo, na forma de ânion molibdato (MoO_4^{-2}), é inserido em uma coluna de troca iônica contendo alumina ($Al_2 O_3$) em condições de meio ácido o que favorece a ligação do ^{99} Mo a coluna. Com o decaimento do ^{99} Mo, através da emissão de partículas beta, ocorre o surgimento do ^{99m}Tc, atingindo sua atividade máxima 23 horas após sua última eluição. A meia vida do ^{99} Mo é de 66 horas, sendo de 6,03 horas para o ^{99m}Tc. O ^{99m}Tc , por sua vez, decai por emissão de fótons gama, produzido o rutênio-99 (^{99}Ru), que é um isótopo estável (ZOLLE, 2007).

Figura 7 - Esquema de um Gerador de Molibdênio/ Tecnécio



Fonte: Lieverson,W., 2012

1.7. Nanotecnologia

Nos últimos anos a nanotecnologia vem ganhando destaque com um investimento considerável para a pesquisa e desenvolvimento de novas estruturas em escala atômica e molecular (EVANS et al., 2018; RAVANSHAD et al., 2018). Com potencial de aplicação em diversas áreas, destaca-se sua aplicação em saúde. (ANDREOU et al., 2017; IQBAL et al., 2018; JONES; SABA, 2011).

As NP's são confeccionadas para serem direcionadas a células e tecidos alvos permitindo a melhora da eficácia, diminuição dos efeitos colaterais e aumento da biodistribuição. As variadas formulações de nanopartículas são investigadas para uso pré-clínico e clínico como sistema de entrega de fármacos como nanorradiofármacos (ARAMI et al., 2019; KHEIRKHAH et al., 2018; MUOTH et al., 2016; UPPAL et al., 2018).

1.7.1. Mecanismo de Absorção de Nanopartículas

As propriedades físico-químicas das NP's e as condições do meio celular influenciam diretamente a sua internalização. Algumas características podem influenciar tal internalização, tais como: tamanho, forma, carga superficial, grupos funcionais de superfície e hidrofilicidade (Figura 8) (COOPER; CONDER; HARIRFOROOSH, 2014; SEVERINO et al., 2011).

O mecanismo de internalização de NPs é descrito na literatura como via endocítica e via não endocítica. Para o mecanismo de via não endocítica, é descrito meios como difusão ou transporte ativo (DING et al., 2015). Na difusão o gradiente molecular de alta concentração é reduzido, isso geralmente ocorre para moléculas pequenas, hidrofóbicas e sem carga. As NPs lipossolúveis também possuem a capacidade se difundir através da membrana (DREIFUSS et al., 2018; DRUDE; TIENKEN; MOTTAGHY, 2017).

Moléculas que apresentam solubilidade em água atravessam membranas de forma passiva através de poros, esse processo é chamado de difusão facilitada (EDGAR; WANG, 2017; HU et al., 2017; SANTAMARIA et al., 2017). Os poros permitem que NPs de uma certa faixa de tamanho e carga elétrica atravessem a membrana. As NPs maiores atravessam a membrana com auxílio de proteínas transportadoras contra o gradiente de concentração (ANSARI et al., 2016; BOYD et al., 2019; LAW et al., 2017).

A via endocítica também apresenta uma dependência relacionada ao tamanho da partícula e das modificações de superfície. As Partículas na escala de micrômetros tendem a entrar nas células através de fagocitose ou macropinocitose (COOPER; CONDER; HARIRFOROOSH, 2014; DARAEE et al., 2016). A fagocitose será a responsável pelo direcionamento e consequentemente, a formação de protuberâncias de membrana que tendem a envolver as partículas e as direcioná-las para o meio intracelular (COOPER; CONDER; HARIRFOROOSH, 2014; LU; LV; LI, 2019; YANG et al., 2019b; ZHANG et al., 2019b).

A macropinocitose se refere a um processo onde há uma regulação por actina. A actina desempenha um papel importante no processo de

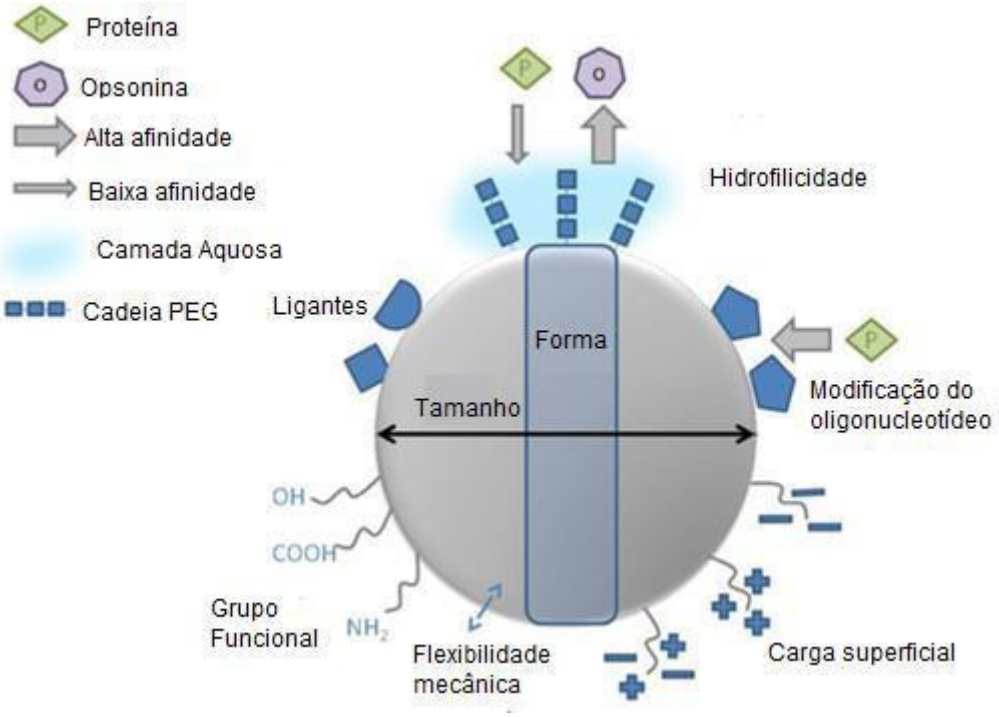
captação e projeção da membrana que será rearranjada e formará microfilamentos capazes de captar o fluido extracelular com as nanopartículas (BARBOSA et al., 2016; COHEN-PFEFFER et al., 2017). O englobamento de uma grande quantidade de fluido extracelular e nanopartículas acontece através do enrrugamento da membrana plasmática (SARAVANAKUMAR; KIM; KIM, 2017; WEI et al., 2016).

Nos processos de endocitose que são mediados por clatrina, a ligação receptor-ligante desencadeia um recrutamento e formação de clatrina no lado citosólico da membrana plasmática. Este tipo de endocitose, mediada por clatrina, é a via endocítica mais comum explorada pelas nanopartículas (COOPER; CONDER; HARIRFOROOSH, 2014; KETTLER et al., 2014; LI; MONTEIRO-RIVIERE, 2016; ZHANG; GAO; BAO, 2015).

Nos processos de endocitose que são mediados por caveolina há uma montagem de camadas de caveolina do lado citosólico da membrana plasmática, que formam uma cavidade de 50 a 80 nm de diâmetro (Figura 9). De maneira geral, tanto a endocitose mediada por clatrina quanto a endocitose mediada por caveolina envolvem diversas cascatas de sinalização bioquímica complexas. No entanto, a entrada de NPs modificadas reguladas por sinalização bioquímica é pouco compreendida (KOCH et al., 2016; LI et al., 2017; TABERNERO et al., 2017).

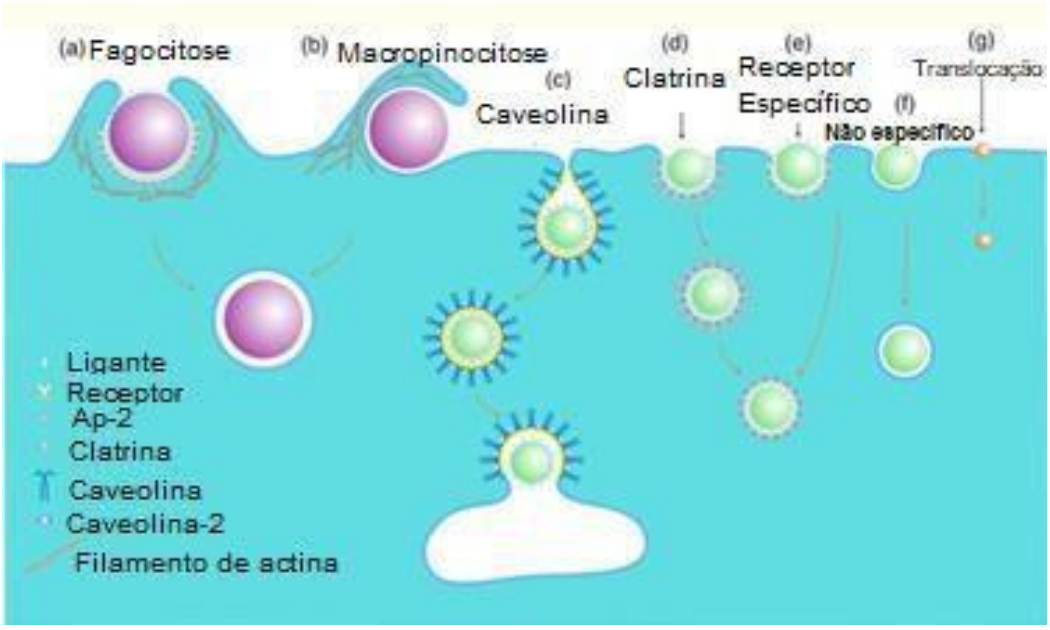
De maneira geral, os nanossistemas administrados por via endovenosa são acumulados na zona do tumor através do efeito de permeação e retenção (EPR) devido à arquitetura dos vasos sanguíneos desses tecidos doentes. A eficácia do efeito EPR está relacionada ao tamanho de partícula, carga de superfície ou hidrofobicidade (COOPER; CONDER; HARIRFOROOSH, 2014; DARAEE et al., 2016; HILL; MOHS, 2016; KARAMAN et al., 2018).

Figura 8 - Propriedades das nanopartículas que influenciam na sua absorção



Fonte: Adaptado de KETTLER et al., 2014.

Figura 9- Vias de internalização de nanopartículas



Fonte: Adaptado de ZHANG; GAO; BAO, 2015.

1.7.2. Nanopartículas Poliméricas

As nanopartículas poliméricas se apresentam como sistemas de carreamento de fármacos com diâmetro inferior a 1 µm. São consideradas nanopartículas poliméricas estruturas como nanocápsula e nanoesferas, que se diferem basicamente em sua composição e organização de suas estruturas (MADKOUR; BUMAJDAD; AL-SAGHEER, 2019; STARSICH; HERRMANN; PRATSINIS, 2019). Esses sistemas são utilizados nas mais diversas aplicações, com a área de vetorização de fármacos se destacando como uma das mais promissoras. (CHAUDHARY et al., 2019; DESALEGN et al., 2019; ISLAM; DMOUR; TAHA, 2019). O destaque no uso de nanopartículas poliméricas se deve principalmente pelas pesquisas que demonstram elevada redução de efeitos adversos, assim como uma baixa toxicidade ao indivíduo e uma grande biocompatibilidade com diversos matérias e fármacos.

Os métodos de preparo destas NP's se baseiam em polimerização in situ de monômeros dispersos ou na precipitação de polímeros, tais como poli(ácido lático) (PLA), poli(ácido lático-co-ácido glicólico) (PLGA), poli(ε-caprolactona) (PCL) (FARAZ et al., 2019; GAKIYA-TERUYA; PALOMINO-MARCELO; RODRIGUEZ-REYES, 2018; MAZUMDER et al., 2019; MOFOKENG et al., 2019).

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1.7.3. Micropartículas

O termo micropartícula faz referência ao tamanho associado a estas estruturas, que pode variar de 1 a 100 µm. (RINTELMANN et al., 2019; YU et al., 2019; ZAHRAN et al., 2019). O uso de sistemas na forma de micropartículas, permite a proteção de fármacos contra fatores externos, assim como: proteção do princípio ativo, mucoadesão e gastrorresistência, melhor biodisponibilidade e maior adesão do paciente ao tratamento, além de permitir a eliminação de incompatibilidade entre ativos e possibilitar uma liberação prolongada (NAGY et al., 2019; WANG et al., 2019d).

Para que o processo de microencapsulação seja considerado ideal é necessário que apresente fatores como: rapidez, simplicidade, reprodutibilidade, baixo custo e apresentar facilidade no escalonamento industrial. Os métodos de encapsulamento baseiam-se na

hidrofilia/lipofilia dos fármacos empregados (ABBASI et al., 2019; BENAMEUR et al., 2019; HODGKINSON et al., 2019; SIERKO et al., 2019a, 2019b; SIWAPONANAN et al., 2019).

1.7.4. Nanorradiofármacos

Os nanorradiofármacos são a associação dos radiofármacos a nanotecnologia, baseados na formação de um sistema nanométrico que contém um ou mais radioisótopos radioativos (COELHO et al., 2015; SANTOS-OLIVEIRA, 2017). (JIMÉNEZ-LÓPEZ et al., 2019; SANTOS-OLIVEIRA et al., 2016). A utilização de sistemas em nanoescalas permite que os radiofármacos permaneçam íntegros, impedindo sua degradação e melhora sua farmacocinética, seu tempo de retenção e captação celular (PORTILHO et al., 2018; SANTOS-OLIVEIRA; STABIN, 2018; SILVA et al., 2017).

2. Objetivo

Desenvolver e caracterizar micropartículas de de Etoposídeo e radiomarcá-las com Tecnécio-99m, para obtenção de agente diagnóstico de tumores de câncer de pulmão em estágios iniciais.

2.1. Objetivos Específicos

- Produzir e caracterizar as micropartículas de Etoposídeo;
- Marcação das micropartículas de Etoposídeo o radionuclídeo Tecnécio-99m;
- Controle de qualidade das partículas radiomarcadas;
- Avaliação das concentrações das micropartículas de Etoposídeo radiomarcadas com Tecnécio-99m nos tumores xenoenxertados em imagens de SPECT;
- Avaliação da biodistribuição das 99mTc-Etoposideo em camundongos Balb/c nude saudáveis e induzidos (xenoenxertados).

3. Materiais e Métodos

A metodologia deste trabalho encontra-se descrita no artigo 1, intitulado *Diagnosing lung cancer using etoposide microparticles labeled with* ^{99m}Tc publicado no *Artificial Cells, Nanomedicine, and Biotechnology* em 2017 de própria autoria.

Para fins de entendimento deste artigo, considerou-se nanopartículas (NP`s) as partículas abaixo de 1 µm de diâmetro. Contudo, uma vez que a distribuição de tamanho das partículas obtidas exibiram estruturas acima de 1 µm, convencionou-se chamar o conjunto de partículas obtidas como micropartículas (MP`s).

4. Resultados e Discussão

Os resultados e discussões deste trabalho encontra-se descrita no primeiro artigo, exibido a seguir, intitulado "**Diagnosing lung cancer using etoposide microparticles labeled with ^{99m}Tc**", publicado no periódico "**Artificial Cells, Nanomedicine and Biotechnology**", em 2017, de própria autoria. Além deste artigo, cujo conteúdo apresenta os resultados experimentais desta tese, um segundo artigo de revisão sobre sistemas de nanopartículas radioativas para aplicações biomédicas encontra-se submetido ao periódico "**Advanced Drug Delivery Reviews**". Este artigo encontra-se submetido até a data de defesa desta tese.

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Diagnosing lung cancer using etoposide microparticles labeled with ^{99m}Tc

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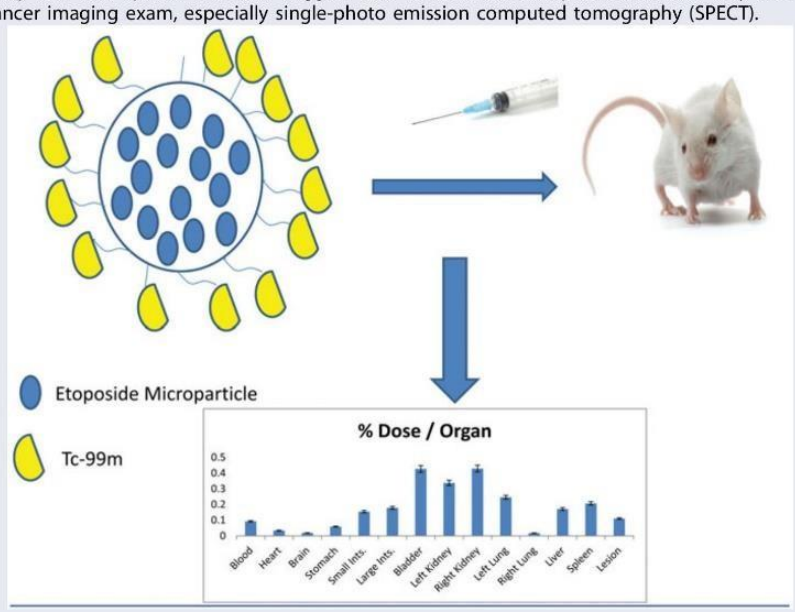
ABSTRACT

The diagnosis of lung cancer mostly occurs when the cancer is already in an advanced stage. In this situation, there are few options for the treatment and most of them have few chances of success. In this study, we developed and tested etoposide microparticles as a diagnostic agent for imaging lung cancer at early stages of development. We tested etoposide microparticles labeled with technetium 99m in inducted mice. The results demonstrated that over 10% of the total dose used was uptake by the tumor site. Also, the results showed that the microparticles had a good renal clearance and low uptake by liver and spleen. The data suggest that these micro-radiopharmaceuticals may be used for lung cancer imaging exam, especially single-photo emission computed tomography (SPECT).



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Radiopharmaceuticals; micro-radiopharmaceuticals; oncology; cancer; nuclear medicine

Introduction

Lung cancer is the most deadly and the leading cancer killer in men since the early 1950s and of women since 1980s. The mortality rate is one the highest, raising this cancer to the fourth position in rank of death by cancer worldwide [1,2]. The lung cancer may be classified into: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC arises in the midlevel airway and is a very aggressive, highly metastasizing and lethal cancer type that comprises 15% of all lung cancers. NSCLC is the major type of lung cancer and comprises 85% of all lung cancers. NSCLC includes lung adenocarcinoma, lung squamous cell carcinoma (LSCC), and lung large-cell carcinoma [3].

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The statistics on cancer are very discouraging, ~13 million new cancer cases and 7.6 million cancer deaths occur each year worldwide [4]. In the last 40 years, the volume of financial resources for treatment, research and prevention of cancer was ~$90 billion [5].

The treatment of lung cancer in USA and Europe remains cisplatin or carboplatin plus etoposide. The etoposide is a chemotherapeutic that works by blocking an enzyme (called topoisomerase II) interacting directly with the ATP-bound enzyme monomer in such a way that each molecule of etoposide stabilizes only a single-stranded break. Depending on the dose of etoposide, single-stranded or double-stranded DNA breaks are generated. Furthermore, the inhibition of topoisomerase II by etoposide is reversible and discontinuation of ternary complex allows quick DNA repair and diminishes the cytotoxicity of the drug, which is necessary for cancer cells to divide and so grow into two new cells. If the enzyme is blocked, the cell's DNA gets tangled up and the cell cannot divides [6,7]. However, lung cancer still has a poor prognosis, with an overall survival at 5 years ~15%. Unfortunately, in most patients (80%), the disease is diagnosed at an advanced stage (III–IV) and less in the early stages (I–II), when it would be potentially curable [2].

Imaging is one of most unique approach to visualize tumors in 3D concept. It may be done, normally, by computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET). However, the first two modalities, i.e. CT and MRI shows a great number of limitations regarding the: (i) minimum detectable tumor (typically $>1\,mm^3$ (and often $>125\,mm^3$), (ii) usefulness to interrogate tumor microenvironment composition; (iii) limited coverage to a few mm^2 and a depth of ~100 μm before resolution is degraded by light scattering [8–15]. On the other hand, the use of techniques that employ radioactive material as imaging methods, like SPECT and PET may overcome this limitation and obtain images of high quality and specificity [14–17], especially with the use of nano and/or microparticles [18–21]. In this direction, we have developed the etoposide microparticle-labeled with ^{99m}Tc as a diagnostic agent for lung cancer in order to develop a new micro-radiopharmaceutical for early, precise and precocious diagnosing of lung cancer.

Materials and methods

Development of etoposide microparticles

The etoposide microparticles were prepared by double emulsion-solvent evaporation method using polycaprolactone (PCL) as polymer. A solution of 50 mg of the drug (etoposide) in 200 μL of 1% polyvinyl alcohol (PVA) aqueous solution was dripped into an organic solution of 50 mg of polymer in 2 mL of dichloromethane under agitation (Ultra-Turrax T10 Basic IKA, Hitachi, Wilmington, NC) for 1 min at 21,200 rpm. This first emulsion was emulsified again with 4 mL of PVA 1.0 wt% solution by homogenization at 21,200 rpm for 2 min to produce a water-in-oil-in-water (W/O/W) emulsion. Then, to form the particles the organic phase was removed by evaporation under reduced pressure during 1.5 h at 25 °C.

Etoposide NPs mean size assessment

Etoposide microparticles size distribution, mean size and polydispersity index (PDI) were determined by dynamic light scattering (DLS) using the equipment Zetasizer Nano ZS (Malvern Instruments, Malvern, UK). Measurements were performed in triplicate at 25 °C and the laser incidence angle in relation to the sample was 173° using a $12\,mm^2$ quartz cuvette. The mean ± standard deviation (SD) was assessed.

Scanning electron microscopy

The morphology of etoposide microparticles were performed by scanning electron microscopy (SEM) (TM 3000; Hitachi). In this study three SEM images were performed, as followed: (i) immediate image (2 h) after the preparation of the microparticle; (ii) 4 h after the preparation of the microparticle and labeled with ^{99m}Tc and (iii) 1 month after the preparation of the microparticle after labeling with ^{99m}Tc.

Labeling with ^{99m}Tc nano-radiopharmaceuticals

The method used was the direct-labeling process as described previously [22–26]. The labeling process used 150 μL of the etoposide microparticles. First, 2 mCi (~300 μL) solution of pertechnetate ($Na^{99m}TcO_4^-$) was incubated with stannous chloride ($SnCl_2$) solution (30 μL/mL) (Sigma-Aldrich, St. Louis, MO) for 20 min at room temperature. Then, this solution was incubated with 150 μL of etoposide microparticles for 10 min, which labeled the microparticles with Tc-99m.

In order to characterize the labeled etoposide microparticles, paper chromatography was made using Whatman paper no 1 (triplicate). The paper chromatography was performed using 2 μl of the labeled nanoparticle in acetone (Sigma-Aldrich, St. Louis, MO) as mobile phase. The radioactivity of the strips were verified in a gamma counter (Perkin Elmer Wizard® 2470, Shelton, CT) after 2 h. In order to confirm the stability of the labeling process of the etoposide microparticles, a lately paper chromatography was performed after 8 h (Tables 1 and 2).

In vivo analysis

Tumor xenograft models

A549 cells (American Type Culture Collection, Manassas, VA) were cultured in RPMI (Gibco/Life Technologies Inc., Rockville,

Table 1. Percentage of labeled etoposide microparticles by ascending chromatograms of ^{99m}Tc compared with free pertechnetate ($Na^{99m}TcO_4^-$) in 2 h.

Time (h)	Labeling (%)±SD
2	99.5 ± 0.4%

Table 2. Percentage of labeled etoposide microparticles by ascending chromatograms of ^{99m}Tc compared with free pertechnetate ($Na^{99m}TcO_4^-$) in 8 h.

Time (h)	Labeling (%)±SD
8	98.9 ± 0.9%

MD) supplemented with 10% of fetal bovine serum (Gibco/Life Technologies Inc.) and 50 μg/mL of gentamicin (Gibco/Life Technologies Inc.). Mycoplasma contamination in cultured cells was excluded using Lonza Mycoplasma Detection Kit (Portsmouth, NH).

Tumors were established by subcutaneous (sc) injection of 2×10^6 A-549 cells at the back of seven 6-week-old male Balb/c nude mice. Tumor size was monitored for 3 weeks and measured by a caliper. The tumor size before imaging was ~2 cm. Mice were observed three times per week for evidence of distress, ascites, paralysis or excessive weight loss.

Biodistribution studies

Evaluation of the biodistribution of etoposide microparticles were made with a Intervention Group using loaded microparticles etoposide labeled with ^{99m}Tc ($n = 7$). Mice were anesthetized with mix solution of 10% ketamine and 2% xylazine in volume of 15 μL and administered intramuscularly (thigh). The micro-radiopharmaceuticals (3.7 MBq in volume of 0.2 mL) were administered by retro-orbital via. Mice were sacrificed by asphyxiation using a carbon dioxide gas chamber after 2 h (120 min) of radio-compound administration. Organs [brain, lungs, kidneys, stomach, small and large intestine, bladder, heart, blood pool and the xenografted tumor (lesion)] were removed, weighted and the activity in each organ, blood and tumor has been counted by a gamma counter (Perkin Elmer Wizard® 2470). The results were expressed as μCi per organ.

SPECT imaging

SPECT were performed to obtain planar images after 120 min retro-orbital injection of the micro-radiopharmaceuticals (3.7 MBq in 0.2 mL), integrating for 5 min the radiation counts centered at 140 KeV, with a Millenium Gamma Camera (GE Healthcare, Cleveland, OH) using a 15% window. The images were done in Balb/c nude mouse inducted with lung cancer as described in xenografted model.

Results and discussion

Etoposide NPs mean size assessment

Etoposide microparticles presented a mean size of 430 ± 10.2 nm, with a PDI of 0.23 ± 0.02 and a unimodal and narrow size distribution (Figure 1).

Scanning electron microscopy

The data from SEM corroborates the data from DLS. Also shows that the etoposide microparticles has a spherical shape and aggregates forming clots with a size range of 450 nm. Is important to notice that although with a higherrate of aggregation in the beging (2 h) it seems that this reach a optimal plateau, and that the aggregation stop trough the time, and after one in one moth is totally stable. Is also important to notice that the presence of ^{99m}Tc does not interfere in the stability or in the morphology of the microparticles, as in the aggregation process (Figure 2).

Labeling with ^{99m}Tc micro-radiopharmaceuticals

The direct method used for labeling etoposide microparticles was a sucess and all the microparticles showed a rate over 99% of labeling (Table 1). The lately paper chromatography (after 8 h of labeling) also showed a great result and confirmed the stability of the labeling process (Table 2).

Biodistribution studies

The result of the biodistribution study is expressed in Figure 3. The results from biodistribution may show several information.

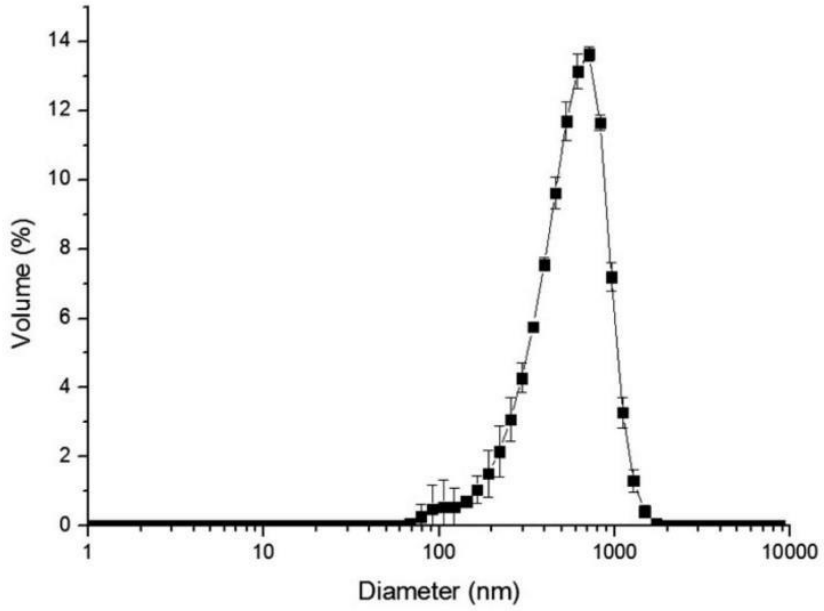

Figure 1. Etoposide microparticle mean size and size distribution.

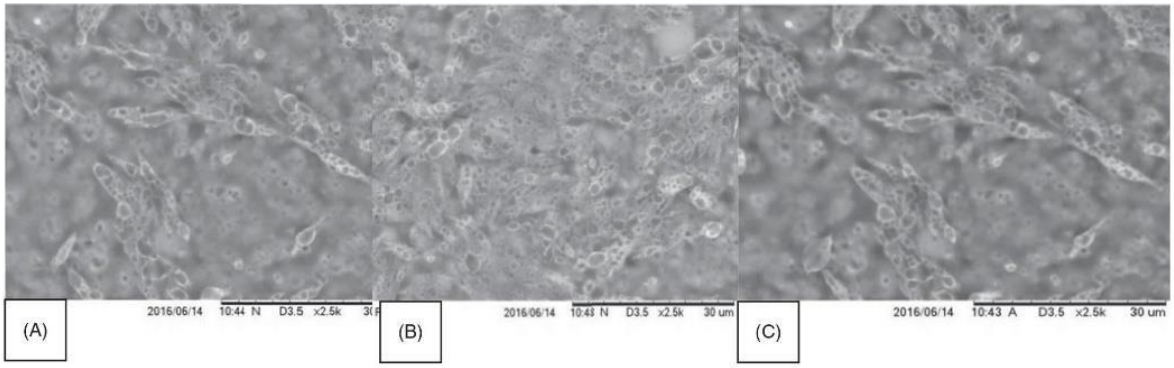

Figure 2. SEM image. The figure "A" is an immediate image, the "B" is after labeling with ^{99m}Tc and "C" is 1 month after labeling with ^{99m}Tc.

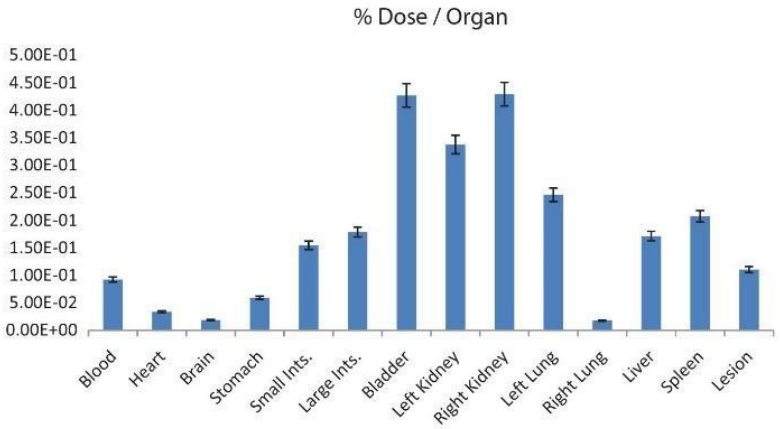

Figure 3. Biodistribution of labeled etoposide microparticles in inducted mice with lung cancer (xenograph model). The *y*-axis is the dose in μCi and the *x*-axis is the organ. Is important to observe that lesion means xenograph lung tumor.

First of all, is possible to observe that a considerable uptake occurred in the lesion (xenografted lung tumor), a total of Σ0.11 μCi. This is almost 15% of the total dose administrated. In general, for acquisition of an imaging is necessary that at least a value equivalent to 5% of the total dose reach the site. So, this result confirmed that this etoposide microparticle may be used as an imaging agent for lung cancer diagnosing. The etoposide microparticles also showed an expressive value Σ0.33 μCi and Σ0.42 μCi in left and right kidney, respectively. This means that the etoposide microparticles have a good renal clearance. These data are corroborated with the findings in bladder Σ0.42 μCi. The high uptake by the left lung Σ0.24 μCi is due the administration via (retro-orbital via). In this way, the drug reaches the blood through the ocular plexus via the vena cava. Once in the vena cava, the first way is the small circulation, reaching first the left lung and then the right lung, thus, we believe that most is retained in the pulmonary alveoli of the left lung due the size of the etoposide microparticles. The uptake by liver and spleen may be explained by the fact that polymeric microparticles could be retained in organs such as liver and spleen. Also, is possible that etoposide microparticles could activated liver macrophages, increasing the uptake by this organ [27,28]. The uptake by stomach and intestines could be explained due the fact that etoposide is substrate of several ABC transporters, notably ABCB1 (MDR1) and ABCC1 (MRP1), ABCC2 (MRP2), ABCC3 (MRP3) and ABCG2 (BCRP), most of them present in intestine and stomach. Nevertheless, etoposide metabolism principally occurs in the liver, but may also happen in other tissues, like intestinal mucosa, since it is *O*-demethylated primarily by cytochrome P450 (CYP) 3A4 and to a lesser extent by CYP3A5 [7]. The uptake by the blood means that the etoposide microparticle have a good interaction with blood proteins and may remain linked to it increasing the circulating time. Finally, the uptake by the brain was negligible.

SPECT imaging

The result (Figure 4) of the SPECT corroborates the findings of the biodistribution, especially the uptake by the tumor and renal clearance due the presence in kidneys and bladder. Is also observed the remaining dose in the top of the image (retro-orbital injection). For this reason, it is not possible to corroborate the negligible uptake by the brain.

Conclusions

The etoposide-microparticle labeled to ^{99m}Tc demonstrated to be a micro-radiopharmaceutical that may be used for early

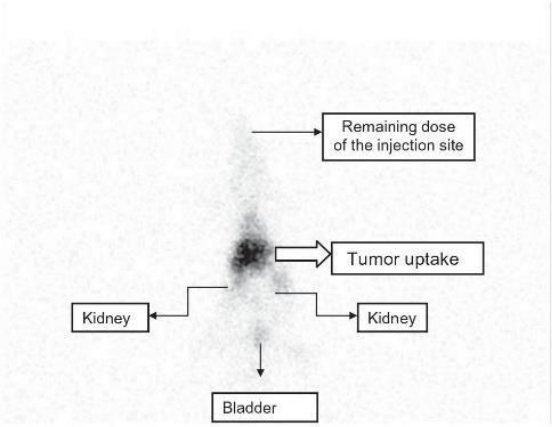

Figure 4. SPECT imaging of Balb/c nude mouse inducted with xenograft cancer model in the back.

diagnosing of lung cancer; nevertheless, the use of a polymeric microparticle showed to be stable and capable to reach the tumor in a high concentration. The biodistribution data also demonstrated that the renal clearance is effective and showed negligible uptake by the brain. The results from SPECT imaging corroborates the biodistribution and also showed the possibility of use of this micro-radiopharmaceutical as imaging agent.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Poly lactic Acid (PLA) and Poly(lactic-co-glycolic acid) (PLGA) Radioactive Nanoparticles used for Biomedical Application

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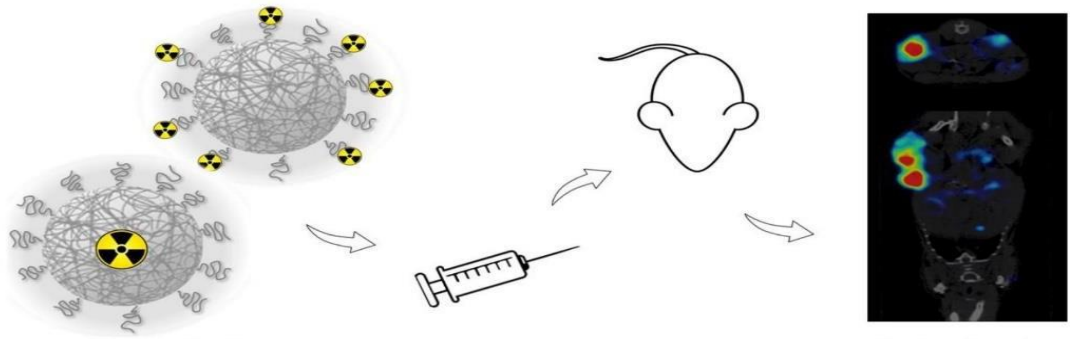
Summary

GRAPHICAL ABSTRACT



Abbreviations

DDS- drug delivery systems
DNA- deoxy-nucleic acid
PHAs- polyhydroxyalkanoates
PLA- polylactic acid
PLGA- poly(lactic-co-glycolic acid)
PGA-poly (glycolic acid)
PDO-poly poly(dioxanone)
PCL-poly (caprolactone)
FDA-Food and Drug Administration
NPs-nanoparticles
PEG-polyethylene glycol
PLLA- poly-L-lactide
PDT-photodynamic therapy
CNT-carbon nanotubes
NSs-nanosystems
SPECT-single-photon emission computed tomography
PET-positron emission tomography
γ- gamma
β- beta
SPIOs-Superparamagnetic iron oxide nanoparticles
TEM-transmission electron microscopy
EPR- enhanced permeability and retention effect
CVD-cardiovascular diseases
CAD-coronary artery diseases
HFIP-hexafluoro-2-propanol
MRSA- Methicillin-resistant Staphylococcus aureus
DMA-2,3-dimethylmaleic anhydride
MDA-MB-231-human breast cancer cell
kDa-kilo Dalton

FITC-fluorescein isothiocyanate
LA-lactic acid
GA- and glycolic acid
PVA-poly(vinyl alcohol)
DCA- dacarbazine
RNA-ribonucleic acid
ANG-angiopep-2
DOX-doxorubicin
EGFR- epidermal growth factor receptor
BBB- blood brain barrier
U87MG -human primary glioblastoma cell line
VEGFR- Vascular endothelial growth factor receptor
PTX-paclitaxel
7721- human hepatocarcinoma cells
A549- human lung cancer
LS174t- colorectal cancer cell
CEA- carcinoembryonic antigen
DTX-docetaxel
MRI-magnetic resonance imaging

ABSTRACT

The most important components of a living cell are polymers. Because of their broad range of properties both synthetic and natural polymers play an essential and ubiquitous role in everyday life. In Drug delivery systems, polymers are essential components, since they exert direct action in the release of the drugs. Recent years have witnessed a growth of research and applications in nanoscience. The reason nanoparticles are attractive for medical purposes is based on their important and unique features, such as their surface to mass ratio, quantum properties and ability to adsorb

and carry other compounds. The aims for nanoparticle entrapment of drugs are either enhanced delivery to target cells and/or a reduction in the toxicity of the free drug to non-target organs. Thus, creation of long-lived and target-specific nanoparticles is needed. Radiopharmaceuticals are molecules linked to radioactive elements, employed in medicine for therapy and for imaging diagnostic. The aliphatic polyester poly(lactic acid) (PLA), the copolymer poly(lactic-co-glycolic acid) (PLGA)are by far the most used bio-absorbable synthetic polymers in the biomedical field. The development of nanoradiopharmaceuticals provides a new paradigm for both Nuclear Medicine and emerges as a viable alternative to the treatment and diagnosis of tumors.

Key words: cancer; nanotechnology; smart device; oncology; nanoradiopharmaceuticals

1. INTRODUCTION

The most important components of a living cell (proteins, carbohydrates, and nucleic acids) are all polymers. A polymer is a large molecule composed of many repeated sub-units[1]. Conjugated polymers are widely propagated for applications relying on their conductivity, photo- or electroluminescence, or light-induced charge generation, such as light-emitting devices and displays photovoltaics or chemical sensors of variable complexity concerning their structure and function [2-8]. Among others, such devices can be advantageous toward inorganic materials in terms of cost and flexibility. The most prominent types of conjugated polymers are polyaniline, polypyrrole, and polyacetylene and derivatives thereof, which have been studied intensely primarily due to their intrinsic conductivity, while polythiophenes, polyphenylenes,polyfluorenes, poly-(arylenevinylene), andpoly-(phenyleneethynylene)have also been studied extensively due to their electrooptical and photoluminescence properties[9].

Because of their broad range of properties both synthetic and natural polymers play an essential and ubiquitous role in everyday life [10]. In nature, polymers are indispensable for construction and as part of the complex cellular mechanism. Polymers range from familiar synthetic plastics such as polystyrene to natural biopolymers such as DNA and proteins that are fundamental to biological structure and function[11]. Polymers, both natural and synthetic, are created via polymerization of many small molecules, known as monomers. Their consequently large molecular mass relative to small molecule compounds produces unique physical properties, including toughness, viscoelasticity, and a tendency to form glasses and semi-crystalline structures rather than crystals. The merge of polymer science with the pharmaceutical sciences has led to a spectacular breakthrough on the innovation (flexibility in fitness, shape, size and surface) in the design and development of new drug delivery systems (DDS) [10].

Polymeric biomaterials and their composites can be classified as biostable, fully biodegradable or partially biodegradable. Biostable polymers are virtually inert, cause minimal tissue response and maintain their properties for years. Partially absorbable polymers are hydrolytically unstable, but since they cannot be fully metabolized by the body and eliminated, they do not dispense the need for the second surgery that removes the implant after tissue healing. Fully absorbable implants are also hydrolytically unstable and have biodegradation characteristics such that they are capable of being totally eliminated by metabolism [12].

In relation to the properties of the polymers, two criteria must be followed in the establishment of a formulation. First, the chemical characteristics of the polymer should not compromise the action of the active ingredients; Second, the physical properties of the polymer must be consistent and reproducible [13].

Polymers degradation are influenced by the following factors: chemical structure and composition of the polymer, physical-chemical factors (ionic charge, ionic strength and pH), physical factors (shape and size), morphology (amorphous, semi-crystalline, crystalline, microstructure), degradation mechanism (enzymatic, hydrolysis, microbial), molecular weight distribution and route of administration [10].

Conventional medicines are characterized by the immediate release of the drug. Technologically, they are easy to prepare, since their production is well established, requiring no sophisticated components and equipment [15]. Polymers are used as excipients in conventional medicament and cosmetic preparations. Conventional solid drugs, such as powders, tablets and capsules, contain polymeric excipients having varying functions. Most often, effective and safe therapeutic responses are achieved by administering traditional medicines. In typical delivery systems, drug concentration reaches a peak shortly after administration and then declines. Levels are dose-dependent and each drug has a therapeutic index above which it is toxic and below which it is ineffective. Otherwise, the optimal therapy requires an advanced drug delivery system [16]. In the revolutionary drugs, polymers are essential components, since they exert direct action in the release of the drugs [17].

By definition, Drug Delivery System is an administration system designed to extend drug release time in the body, sustain its plasma concentration and control the temporal and spatial location of the molecules in vivo [15;18;19]. Thus, cyclic fluctuations in the concentration are eliminated and the biological availability of the drug is increased. Also, reduction of toxicity and decrease in the number of daily doses can be achieved [20-22]. In addition to presenting modified release of the drug, the manufacture of DDS often requires the use of specific equipment, processes and components [21;23]. The development of modified release systems for drug

181 establishment is an interesting strategy for this purpose. Such systems include
182 drug/polymer conjugates, polymer micelles, liposomes, and nanoparticles [24].

183 The biodegradation of the polymer is a process in which the macromolecule is
184 converted into simpler products, either by the action of enzymes or microorganisms, or
185 by hydrolysis of the chain in aqueous media [25]. Thus, biodegradable polymers have
186 an advantage over non-biodegradable polymers, since they are fully absorbed by the
187 body, requiring no further removal [26].

188 Biodegradable polymers are of significant interest to a variety of fields including
189 medicine, agriculture, and packaging. One of the most active areas of research in
190 biodegradable polymer is in controlled drug delivery and release. Biodegradable
191 polymers have an innumerable uses in the biomedical field, particularly in the fields
192 of tissue engineering and drug delivery [27;28]. In order for a biodegradable polymer to
193 be used as a therapeutic, it must meet several criteria: 1) be non-toxic in order to
194 eliminate foreign body response; 2) the time it takes for the polymer to degrade is
195 proportional to the time required for therapy; 3) the products resulting from
196 biodegradation are not cytotoxic and are readily eliminated from the body; 4) the
197 material must be easily processed in order to tailor the mechanical properties for the
198 required task; 5) be easily sterilized; and 6) have acceptable shelf life [27].

199 Different classifications of various biodegradable polymers have been proposed
200 according to their synthesis process (Figure1): (i) polymers from biomass such as
201 biopolymers from agro-resources (e.g., starch or cellulose), (ii) polymers obtained by
202 microbial production such as the polyhydroxyalkanoates (PHAs), (iii) polymers
203 conventionally and chemically synthesized from monomers obtained from agro-
204 resources, e.g., the polylactic acid (PLA), and (iv) polymers obtained from fossil
205 resources. Only the first three categories (i–iii) are obtained from renewable resources.

We can further classify these biodegradable polymers into two main categories: the agro-polymers (category i) and the biodegradable polyesters or biopolyesters (categoriesii–iv) [29].

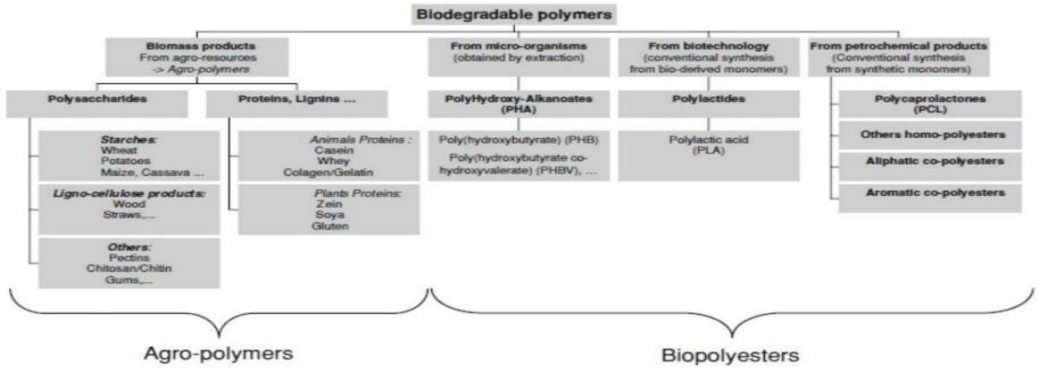


Figure 1. Classification of the main biodegradable polymers [29].

Structurally, biodegradable polymers possess bonds (i.e., ester, amide, or ether bonds) which are cleavable enzymatically or hydrolytically. A polymer with a C-C backbone can resist the degradation. Depending on the structural properties of the polymer, a heteroatom-containing polymer presents different degrees of biodegradability. Based upon their synthesis methodologies, biodegradable polymers can be classified into (i) natural (e.g., fibrin, collagen, cellulose, hyaluronan, pectin), (ii) semisynthetic (e.g., chitosan), and (iii) synthetic [e.g., poly(lactic acid)(PLA), poly(glycolic acid)(PGA), poly(lactic-co-glycolic acid) (PLGA), poly(dioxanone) (PDO), poly(anhydrides) and poly(ortho esters) [24].

Poly (hydroxyalkanoates) - hydroxy acid polyesters - are optically active, stereo-regular biopolymers produced by biosynthetic route from natural sources. Poly (hydroxybutyrate) and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) copolymer have

been studied in the preparation of DDS. The use of these polymers may represent a lower cost when compared to other conventional biodegradable polymers [30]. Aliphatic polyesters are the polymers which undergo biodegradation in biological medium, being more studied in drug delivery systems. It includes: poly (lactic acid) PLA, poly (glycolic acid) PGA, poly (caprolactone) (PCL) and copolymers of lactic and glycolic acids (PLGA) [30-32].Therapeutic polymers are those to which therapeutic properties are attributed. Management of structure of synthetic polymers allows them to bind to specific receptors, present in pathogens or cells, promoting recognition, triggering the modulation of cell function [34-36].

Until 1960, hydrolytically unstable polymers were considered a terrible discovery. However, with the advancement of research, these materials arouse interest in the medical and pharmaceutical areas especially due to the possibility of being used in temporary implants (e.g. sutures, staples and nano-reservoirs). Poly (lactic acid) (PLA) and Poly (lactic acid-co-glycolic acid) (PLGA) are relatively hydrophobic polyesters, unstable in humidity, biodegradable and produced from renewable resources easily. Polymers derived from lactic and glycolic acids have received a lot of attention in the research of alternative biodegradable polymers, and have already been approved by the Food and Drug Administration (FDA) for use as DDS.

In contrast to the great amount studies of the preparation of conjugated polymers and their properties in the bulk or in thin films, nanoparticles of conjugated polymers have been relatively little addressed[9;37-39]. To render the term more precisely, a nanoparticle is considered to be a sub-micrometer entity which represents a separated continuous phase, surrounded by a continuous free-flowing medium (usually a low-molecular-weight liquid, most often water) or placed on a surface. Although the definition identifies nanoparticles as having dimensions below 0.1 μm or 100 nm,

especially in the area of drug delivery relatively large (size >100 nm) nanoparticles may be needed for loading a sufficient amount of drug onto the particles [40-43].

Recent years have witnessed a growth of research and applications in the area of nanoscience. Anticipated uses in medicine include drug delivery, diagnostics, nutraceuticals and production of improved biocompatible materials [42;44;45]. The reason why these nanoparticles (NPs) are attractive for medical purposes is based on their important and unique features, such as their surface to mass ratio that is much larger than that of other particles, their quantum properties and their ability to adsorb and carry other compounds. The composition of the nanoparticles may be of biological origin like phospholipids, lipids, lactic acid, chitosan, or have more "chemical" characteristics like various polymers, carbon, silica, and metals. The aims for nanoparticle entrapment of drugs are either enhanced delivery to target cells and/or a reduction in the toxicity of the free drug to non-target organs. For these aims, creation of long-lived and target-specific nanoparticles is needed.

Nanoparticles administered by the oral route can follow different routes: direct transit in the TGI until elimination by the feces, bioadhesion (adhesion to the intestinal mucosa) and absorption, being the first two routes most important [46]. Thus, rising bioavailability of drugs inserted in nanoparticles is the result of a longer contact time of the drug with the intestinal mucosa due to their increased relative surface area.

Bioadhesion is a process by which particles are immobilized on the intestinal surface by an adhesion mechanism. This mechanism extends the time of interaction of a drug at the site of action and improves the absorption [46].Gut mucus is composed of high molar mass glycoproteins that allow adhesion by nonspecific interactions of the polymer nanoparticles through hydrogen bonds or Van der Waals forces [46]. Adhesion is optimized when the polymer is dry, but oral administration causes the particles to mix

with the endogenous liquids. Bioadhesion may also occur through specific interactions between intestinal cells and carriers through cell membrane receptors. In this case, it is possible to use clusters attached in the polymeric walls that allow a specific interaction with the target receptors. However, these mechanisms are more difficult to happen due to the limited diffusion of the particles through the mucus [46].

One of the complications in the use of particulate drug carriers including nanomaterials is the entrapment in the mononuclear phagocytic system as present in the liver and spleen [19; 47-50]. Surface modification with polyethylene glycol (PEG) extended the presence in the circulation by inhibiting recognition and phagocytosis by the mononuclear phagocytic system [51-53]. In addition, when gold nanorods were modified using PEG, it altered the distribution and reduced the in vitro toxicity [53].Although nanoformulation is aimed at enhancing drug delivery without loss of drug activity. In a study comparing insulin-chitosan nanoparticles to chitosan solution and chitosan powder formulations, the insulin-chitosan nanoparticles were less effective in terms of bioavailability and lowering blood glucose level in both a rat and sheep model [54]. NP size influence its distribution and bioavailability as demonstrated for lipid vesicles for which a lower liver uptake was found for the smaller vesicles (200/300 nm versus 25/50 nm) [54-56]. For liposomes with sizes >100 nm the clearance rate by the mononuclear phagocytic system increased with increasing size, while for sizes below 100 nm charge was more important [57].

Physical degradation such as heating and light may be used to provoke the therapeutic effect or for local drug release, respectively. Thermosensitive nanoparticles may be used for selective release of the content after specific localization. For example, doxorubicin-enhanced cytotoxicity was observed in vitro at 42 °C compared to 37 °C using copolymers of polyethylene glycol (PEG) and poly-L-lactide (PLLA) (Na et al

2006). In addition, the release of photosensitizers from nanoformulations by light, (photodynamic therapy-PDT), was able to induce cytotoxicity [58;59].

One of the major challenges in drug delivery is to get the drug at the place it is needed in the body thereby avoiding potential side effects. The entrapment of chemotherapeutics in nanosized formulations like liposomes has been already subject of study for considerable time [60-61]. Liposomes nanostructures have the advantage of being small, flexible and biocompatible thus being able to pass along the smallest arterioles and endothelial fenestrations without causing clotting. Also, other material as (co)-polymers and dendrimers at the nanosize range alters the distribution of encapsulated or attached drugs. The nanoparticle formulation resulted in paclitaxel-enhanced cytotoxicity for tumor cells *in vitro* and improved therapeutic efficacy in an *in vivo* animal model [63]. Paclitaxel encapsulated in vitamin E TPGS-emulsified poly (D,L-lactic-co-glycolic acid) (PLGA) nanoparticles resulted in a higher and prolonged level above the effective concentration *in vivo*.

There is a concern of how the body behaves with these nanomaterials. Once in the body nanoparticles must be monitored because due to the small diameter it can accumulate in the body and not be eliminated [64]. This is particularly true for the applications of nanoparticles for drug delivery. In these applications particles are brought intentionally into the human body and some of these new applications are envisaged an important improvement of health care. Opinions started to divert when toxicologists claimed that new methods and protocols are needed [65-68].

When nanoparticles are used for their unique reactive characteristics it may be estimated that these same characteristics also have an impact on the toxicity of such particles. Carbon derived nanomaterials showed that platelet aggregation was induced by both single and multi-wall carbon nanotubes, but not by the C_{60}-fullerenes that are

used as building blocks for these carbon nanotubes(CNT) [69]. Silica nanoparticles of 15 nm and 46 nm showed similar dose dependent cytotoxicity *in vitro* [70]. However, for cationic silica nanoparticles using amino-hexyl-amino-propyltrimethoxysilane as a surface modification, no cell toxicity was detected [71]. The amount of data about NPs toxicity is based on a small panel of NPs (combustion derived NPs and TiO_2) and the premise that the effects observed by particulate matter are driven by the ultrafine particle fraction in it [72].

A great number of biodegradable polymers have been synthesized in natural environment during the growth cycles of organisms. Biodegradable polymers are considered as ideal biomaterials for the development of controlled sustained-release DDS as well as therapeutic devices such as degradable implants, impermanent prostheses, and degradable 3D scaffolds for tissue engineering [73-75].

Some aspects such as the toxicity of the solvents used and the efficiency of the encapsulation of the desired material must be observed when formulating polymeric nanoparticles. Monomers polymerization allows the "design" of the material to be obtained, since the synthesis of the polymer is being carried out at the same time as the encapsulation. In situ polymerization is a technique that can be carried out by different routes, with emulsion, mini-emulsion and microemulsion polymerization being the most used [76]. The most common nanoparticle preparation process in the pharmaceutical field is the solvent evaporation technique [76-78].

The choice of the method of preparation should consider the nature of the polymer and the drug and also the route of administration. The final product should have the following characteristics: (i) Maintenance of the stability and activity of the drug; (ii) High encapsulation efficiency, as higher the concentration of encapsulated drug, the amount of nanoparticles to be used in the pharmaceutical forms will be lower;

(iii) Low polydispersity in size; (iv) Reproducible drug release profile, so that the nanoparticles always show similar dissolution kinetics; (v) micro/nanoparticles must do not present aggregation or adhesion, since these factors causes the loss of product and difficulties of adjusting the dose. [79].

The biodegradable polymers are also bioactive and hence can be used as polymer-therapeutics which can also be exploited for targeted delivery of a wide range of small and large molecules in a controlled, sustained or pulsatile manner. Biodegradable polymeric nanoparticles (NPs) and nanosystems (NSs) are supposed to be very efficient drug delivery systems (DDSs) that are extremely safer than any other non-biodegradable polymers and lipids used for gene/drug delivery [80-82].

Nanoparticles administered intravenously concentrate mainly in the liver, spleen and bone marrow, by the mononuclear phagocytosis. These organs function as reservoirs, causing the nanoparticles to rapidly disappear from the circulation. Thus, one should be concerned with the accumulation, elimination and degradation of these systems [83].

2. RADIOACTIVE NANOPARTICLES

Nuclear imaging modalities include single-photon emission computed tomography (SPECT) and positron emission tomography (PET) as tools to visualize *in vivo* abnormalities. Nuclear imaging is noninvasive and provides high sensitivity for detection of biological processes, especially in diagnosing and staging disease states. Several radiopharmaceuticals have been approved by the Food and Drug Administration (FDA) for use in humans. However, selective delivery of a radioisotope to visualize a particular region of interest remains a challenge. In this context, nanoparticles (NPs) have emerged as promising vehicles to transport radioisotopes to desired sites within the

body [84, 85].Several FDA-approved contrast agents and molecular imaging probes and contrast agents are listed in the Molecular Imaging and Contrast Agent Database (MICAD) [85].

Radiopharmaceuticals are molecules containing at least one radioactive element that emits useful radiation, employed for therapy and for diagnostic imaging in Nuclear Medicine. Radiopharmaceuticals are typically constituted of two components: carrier (particles) and radionuclide, and it is directly related to the radioisotope used [86]. However there are also "pure" radiopharmaceuticals, as Na[18]F, [223]RaCl2 Na[131]I where no carriers are needed

Radionuclide characteristics are responsible for the application and indication of the radiopharmaceutical. For diagnostic applications in Nuclear Medicine, radiopharmaceuticals based on nuclides providing an emission of gamma radiations (γ, $E \approx 140$ keV) or a positron (β^+, $E \approx 511$ keV)should be employed [87]. Thus, after administration, the radiopharmaceutical penetrates the tissues and its radiation is measured by means of single photon detection (SPECT) or a detection of β^+/electron annihilation, which generates two coincidence γ radiations (PET). This procedure allows evaluating the biodistribution of the radiopolymer and locating the foci where it was most captured [88].The ideal radiopharmaceutical reaches the tissue target avoiding that the radiation spreads to other tissue around. In addition, a radiopolymer should remain in the body for a period short enough to avoid prolonged exposure of the patient to radiation, but long enough to allow the acquisition and processing of images, as well as to develop its therapeutic action [89].

Radioactive NPs for imaging can be designed by two possible methods (Figure 2). The first method involves incorporation of a radioactive element into a nanosized cluster. Despite the advantageous of this method, many radioactive elements tend to get

oxidized at the nano level and subsequently elude the properties associated with nanoscale imaging. Noble metals such as gold can be bombarded with neutrons in a nuclear reactor to generate radioactive core NPs. The second method involves attaching a radioactive element to a NP (also called radiolabeling of a particle). This method is versatile and can incorporate various radioelements of choice into a ligand on the NP surface. In this method multi-carboxylate ligands are grafted on the surface of the NP. Subsequently, these chelators are used to carry metallic radionuclides [85]. However, the dissociation of the radionuclide under *in vivo* conditions could result in a false imaging [85].

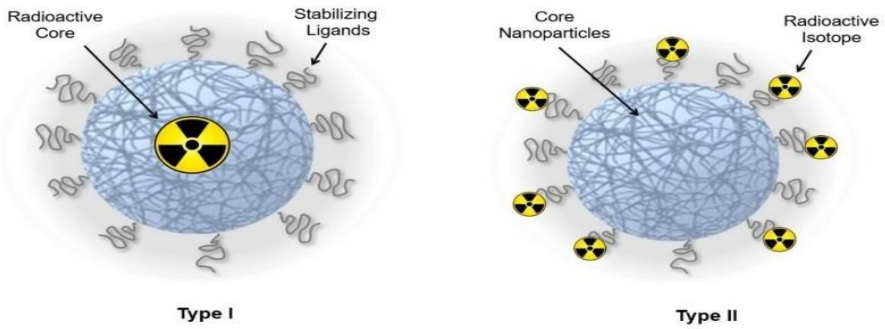


FIGURE 2: Schematic of radioactive polymer nanoparticles**.** In the Type I configuration, the radioactive elements incorporated into a nano-sized cluster, whereas in the Type II configuration, the radioactive element is decorated onto the nanoparticle surface.

Iodine 131 (^{131}I) is a commonly used radioisotope; The γ (gamma) emission of ^{131}I can be used for imaging and β (beta) for therapy, but the release of ^{131}I and ^{131}I-tyrosine in the blood poses a potential health hazard [85].

As reviewed by Psimadas et al. [91], ^{111}In-labeled NPs have been widely used to understand the biodistribution of NPs. For this purpose, polymeric and micellar NPs have been labeled with ^{111}In. Also, NPs of carbon, gold, or iron oxide were labeled with ^{111}Infor understanding the biodistribution or evaluating disease states.

The ^{64}Cu is one of the most studied isotopes of copper, mainly due to its potential in imaging and therapy applications. Its decay occurs by three processes: positron, electron capture, and beta decays. Superparamagnetic iron oxide nanoparticles (SPIONs) have been functionalized with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and radiolabeled with ^{64}Cu [7]. In this study, micelle-coated SPIONs were synthesized by treating 6.2nm sized SPIONs with polyethylene glycol (PEG) derivatives, amino-PEG2000 and mPEG5000 phospholipids. The amino groups on the lipids were utilized to attach DOTA ligands to the surface. After coating with phospholipids, the hydrodynamic size of SPIONs increased from 7 to 20 nm. DOTA ligands on the surface of SPIONs were subsequently used to radiolabel with ^{64}Cu. The resultant conjugate showed excellent stability for 24 hours in mouse serum. Finally, ^{64}Cu labeling of the NP was achieved by mixing ^{64}Cu in acetate buffer with DOTA-functionalized polymeric nanoconjugates. Nonspecifically bound ^{64}Cu to amide and ester groups was removed by treating the radiolabeled NPs with DTPA with subsequent removal of DTPA-^{64}Cu complexes by Centricon separation [92,93]

^{18}F-labeled radiopharmaceuticals was synthesized by paramagnetic iron oxide NPs using ‘click’ chemistry, a condensation of azide and alkyne groups catalyzed by Cu(I). In this study, aminated-cross-linked dextran iron oxide NPs of an average size of 30 nm, containing40 primary amines per particle, were used. As a first step, five

primary amine groups in each NP were used to functionalize with a fluorescent dye, Vivotag-680.The remaining primary amino groups present on the surface of the iron oxide NPs were derived to anazide functional group. Subsequently, azide groups on the NPs were chemoselectively reacted with propargyl^{18}F-PEG3 in the presence of catalytic amounts of copper salts to obtain ^{18}F-labeled iron oxide NPs in 99% radiochemical purity within 120 min. In the absence of copper salts, however, ^{18}F labeling could not be achieved [94;95].

Technetium-99m is the most widely used SPECT radionuclide because it possesses optimal imaging characteristics, including a short half-life of 6.0 h and a γ emission of 140 keV for SPECT imaging applications. NPs have been labeled with ^{99m}Tc to expand understanding of their biodistribution characteristics. Radiolabeling with ^{99m}Tc has usually been accomplished using two different methods. In the case of iron oxide NPs, direct labeling with ^{99m}Tc was performed by Madru et al. and Fu et al [96;97].However, other metallic or polymeric NPs have been modified by both the direct labeling approach and hydrazine nicotinic acid (HYNIC)-type ligand systems for labeling with ^{99m}Tc. In the case of direct labeling, superparamagnetic iron oxide nanoparticles (SPIONs) were treated with $^{99m}TcO_4^-$ in the presence of stannous chloride as the reducing agent [96]. Using this method, 99% radiolabeling was achieved.Technetium-99m-SPIONs showed homogenous size distribution with a mean diameter of 13 nm, as measured by transmission electron microscopy (TEM)studies. The zeta potential of the conjugate was between 5 and 15mV at pH 4–6. In another study,$CoFe_2O_4$ NPs were directly labeled with ^{99m}Tc using$SnCl_2$ [98]. In this method, the conjugates were stabilized using ethyl 12-(hydroxyamino)-12-oxododeconate,poly-(lactic-co-glycolic acid) (PLGA) and bovine serum albumin. The average hydrodynamic diameter of NPs increased from 106 to 160.8 nm after labeling with ^{99m}Tc. The zeta

potential remained constant(−23.6 to −23.8mV) after labeling. This study demonstrated that direct labeling of SPIONs with $Na^{99m}TcO_4$ using a $SnCl_2$ reducing agent provides high yields. This technique is easy to translate into clinical settings.

Technetium99 metastable radionuclide (^{99m}Tc) stands out because it is used in 90% of diagnostic procedures in Nuclear Medicine [99]. Nanorapharmaceuticals based on Technetium-99m and, more recently, to Rhenium-186 have become important tools for the diagnosis and therapy of various diseases or dysfunctions of organs and systems that make up the human body [100-102]. Development of nanoradiopharmaceuticals provides a new paradigm for both Nuclear Medicine and Radioprotection and Dosimetry and emerges as a viable alternative to the treatment and diagnosis of tumors [103;104].

Others radiopolymers - all labelled with beta emitters – are currently used in the treatment of bone pain caused by Bone Metastasis [105].

a. Polymeric nanostructures use in therapy

Polymeric nanostructures have the potential to improve the medical outcomes of various therapeutics and diagnostics by enhancing the accumulation of the embedded active species into the target sites of diseased tissues via passive and/or active targeting. They can also be utilized for combinational therapy/diagnosis. In passive targeting, nanoparticles accumulate into pathological sites with leaky vasculature (e.g. tumor and inflammation sites) due to the EPR (enhanced permeability and retention) effect, whereas active targeting is achieved through decorating the surface of nanoparticles with targeting ligands that bind to receptors overexpressed on the diseased tissues. Active targeting features can also be incorporated into the nanostructures via including

494 stimuli-responsive components into the nanomaterials. Ideally, both targeting
495 mechanisms aim to concentrate the nanomaterials, while containing the embedded drugs
496 and/or diagnostic probes, at the diseased tissues and avoiding accumulation or drug-
497 release at healthy tissues.

498 Biodegradable scaffolds composed of PLA and β-tricalcium phosphate is
499 developed for complex maxillofacial reconstruction. Biocompatibility tests with
500 mesenchymal stem cells indicated better proliferation, without toxicity. The porous
501 interconnected structures make possible cellular adhesion and vascular proliferation.
502 The in vivo investigation in rats led to complete bone ingrowth within 30 days with
503 minimal inflammatory impacts [106]. A study reported the development of NPs targeted
504 to regions of vascular angiogenesis in the course of reperfusion and re-oxygenation of
505 ischemic tissue [107].

506 Recent advances in the field of nanotechnology can be applied to pharmacology
507 to solve the above problems and have proved to be excellent tools to treat different
508 diseases [108].

509

510 ***2.1.1 Cardiovascular diseases***

511 Cardiovascular diseases are the number one death-causing disease and according
512 to the World Health Organization, in 2012, 3 in every 10 people worldwide died from
513 cardiovascular diseases (CVD).44 In the United States, in 2010, more than 300 billion
514 dollars were spent on medical expenses due to CVD.45 Diseases related to the
515 cardiovascular system include atherosclerosis, hypertension, and coronary artery
516 diseases (CAD), which could result in heart attack or stroke.

517 Polymeric nanoparticles with specific biomarkers have been highly investigated
518 in medical imaging for diagnosis and treatment of cardiovascular diseases, such as,

519 atherosclerosis, hypertension, and coronary artery diseases [109-113]. In their previous
520 studies, Col IV-targeting peptide conjugated-polymeric nanoparticles encapsulated with
521 paclitaxel reduced the thickness of neointima to 50%, compared to a carotid injury
522 model control group [114;115].

523 The first generation of DES (drug-eluting stents) effectively reduced restenosis,
524 but profoundly delayed healing. Oh and Lee reported the preparation of nanofibers as a
525 drug (β-estradiol) eluting coating on a stent. They used Eudragit S-100 (ES) as a
526 nanoparticle (NP) base, and the mixtures of hexafluoro-2-propanol (HFIP), PLGA and
527 PLA as a nanofiber base at tunable ratios [116].

528 Col IV-targeting peptide conjugated-polymeric nanoparticles encapsulated with
529 paclitaxel reduced the thickness of neointima to 50%.Results showed that the peptide
530 treatment using polymeric nanostructures and specific targeting have potential for
531 treatment of inflammation-involved diseases like atherosclerosis[114;115;117].

532

533 ***2.1.2. Infectious diseases***

534

535 Infectious diseases are usually caused by bacteria, viruses, parasites or fungi.
536 They usually spread from one to another, and, sometimes, could become serious,
537 difficult to treat, and life-threatening. Since the expansion of the global transport
538 network, infectious diseases have become more broadly transmissible, increasing the
539 urgency to develop efficient treatment methods [118].

540 Although there are several therapeutics and diagnostics that have been tested
541 with varying degrees of success for management of infectious diseases, the poor
542 bioavailability and serious side effects of some of these agents compromise the expected
543 therapeutic outcomes [119-121]. Nanoparticles have been utilized to improve delivery

544 efficiency of antimicrobials to the site of infection, together with the use of auxiliary
545 devices for localized delivery[122-124]. Nanoparticles could improve the stability and
546 pharmacokinetics of the encapsulated antimicrobials, allow prolonged retention and
547 sustained release of the drugs at the sites of infections, and overcome the drug resistance
548 of the bacteria [126-130].Cationic cobaltocenium polymers were prepared to treat
549 MRSA (Methicillin-resistant Staphylococcus aureus) infection [131]. Ionic
550 complexation between cationic metallopolymers and carboxylate in β–lactam antibiotics
551 inhibited β–lactamase activity to protect β–lactam antibiotics from hydrolysis, which
552 improved antimicrobial efficacy. Fully degradable polymeric nanoparticles were then
553 developed and their antimicrobial activities were evaluated in vitro against
554 Staphylococcus aureus and Escherichia coli [132].
555
556 ***2.1.3. Cancer***
557 Tumor is a disease characterized by uncontrolled growth of cells, where this
558 group of cells might have the ability to spread in the body through the blood and lymph
559 systems. The main characteristics of cancer are sustaining proliferative signaling,
560 evading growth suppressors, avoiding immune destruction, enabling replicative
561 immortality, promoting inflammation, invading and metastasizing, inducing
562 angiogenesis, accruing genome instability and mutation, resisting cell death, and
563 deregulating cellular energetic, which are shared by more than 100 cancer-related
564 diseases [133]. These diseases can be categorized by the type of cell or tissue in which
565 cancer originates. Cancer usually acquires these characteristics due to genetic and
566 epigenetic alterations, which consequently result in molecular variations, such as,
567 overexpression of receptors and proteins, changes in upstream and downstream
568 effectors, and tumor progression [134-137].Cancer treatment include surgery,

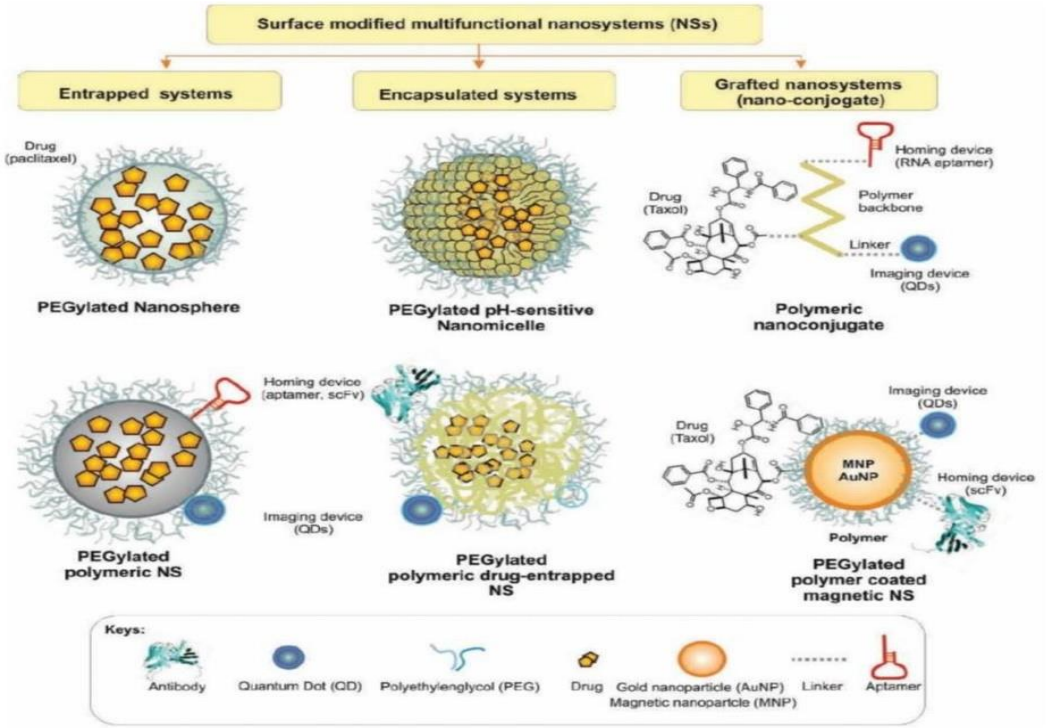
chemotherapy, radiation therapy, hormonal therapy, immunotherapy, hyperthermia, stem cell transplantation, photodynamic therapy and laser surgery. Besides, more than one strategy can be combined together, depending on the type and stage of cancer. To date, complete removal of cancerous tissues remains a challenge [138].

The two main goals for the treatment of cancer with various therapeutic agents are the selective delivery of drugs to the target sites and interfering with molecular events involved in the cancer progression without affecting normal healthy cells. The ^{64}Cu-labeled RGD-targeted carbon nanotubes and non-targeted gold nano shells were each evaluated in a mouse model of brain cancer, showing efficient tumor uptake at 6–24 h [139-140].Although nanoparticle-based formulations for treatment of cancer have been showed greater efficacy *in vitro* and *in vivo*, conversion of those promising pre-clinical results to successful clinical trials has been challenging. Only few nanoparticulate systems have been approved for clinical usage [*e.g.* Abraxane®, DaunoXome®, DepoCyt®, Doxil®/Caelyx®/Myocet®] and few additional candidates are undergoing clinical trials [*e.g.* BIND-014 (Phase 2), NC-6004 (Phase 1/2), NK012 (Phase 2), NK105 (Phase 3), CRLX101 (Phase 2), PK1 (Phase 2)] [138].

One of major challenges in nanoparticle-based drug delivery in cancer therapy is the incompatibility between prolonged blood circulation for EPR (enhanced permeation and retention) effects, which requires neutral or slightly negative surface charges, and efficient tumor cell uptake, in which positive surface charges are preferred. Two strategies, switch of surface charge and removal of stabilization layer, have been applied to address this issue [138]. Polymeric nanostructures, capable to adjust their surface charge to the surrounding pH conditions, were prepared by self-assembly of block copolymers comprised of a hydrophilic zwitterionic polyphosphoester block and a hydrophobic PCL segment [PCL-*b*-P(AEP-*g*-TMA/DMA)]. The zwitterionic surface

enabled elongated circulation of the nanocarriers in blood. Once they reached tumor sites, however, cleavage of amide bonds between 2,3-dimethylmaleic anhydride (DMA or DMMA) and primary amine under acidic tumor extracellular environment, decreased the anionic character in the zwitterionic segments and resulted in positively-charged nanoparticles that could be internalized more easily into tumor cells [141]. In another study, Doxorubicin-loaded into these nanoparticles inhibited growth of human breast cancer cell MDA-MB-231 xenografts in nude mice[142].

Bioabsorbable polymers in DDS can be defined as polymers that undergo transformations in the biological environment by, for example, phagocytosis, through cellular activity [80]. Advanced biodegradable NSs (Nanosystems) have the ability to penetrate into tumor and target the cancer cells only with no or little effects on the healthy cells [143-146].Figure3 represents schematic structures of advanced DDSs and multifunctional NSs used for targeted therapy of cancer.



607 **Figure 3**. Schematic illustration of advanced multifunctional drug delivery systems
608 [80].
609
610 Furthermore, the biodegradable polymeric carriers have been modified by tumor
611 targeting agents to enhance the NPs translocation into tumor cells. PEG-PCL-PEG
612 thermo-sensitive hydrogel containing a tumor-targeted biodegradable folate-poly(ester
613 amine)/DNA complexes has been synthesized and investigated for targeted gene
614 delivery. The hydrogel composite indicates slight cytotoxicity with high transfection
615 efficiency *in vitro* [80].
616
617

3. NATURAL NANOPOLYMERS

Natural polymers can be divided into two main classes: proteins and polysaccharides. Albumin and gelatin are the proteins with more relevance for the preparation of DDS for cancer therapy [24]. Gelatin is a protein obtained by the thermal denaturation of animal collagen, in which the triple helix of collagen is broken giving water-soluble strains. Gelatin is a poly-ampholyte whose structure comprises cationic and anionic groups, along with the hydrophobic groups. Because of its biodegradability and biocompatibility, gelatin has been used in the development of DDS for different biomedical applications, namely cancer therapy [147]. Albuminis the most abundant protein in the human blood plasma, accounting for 50 % of its total mass. It presents a molecular weight of about 66.5 kDa and a diameter of7.2 nm. Albumin is a hydrosoluble protein, is stable in a pH range of 4 to 9, and can be heated at 60 °C for up to 10 h without deleterious effects. Human serum albumin (HSA) has a multitude of functions in the human body. To mention: solubilization of long chain fatty acids, binder for bilirubin (resulting from heme breakdown), transport of metal ions (copper(II), nickel(II), calcium(II), and zinc (II)) in the bloodstream, and major responsibility for colloid osmotic pressure of the blood, and upon hydrolytic breakdown[32;148]. Inthe development of DDS for cancer therapy, the use of albumin brings some advantages since this protein isused by the proliferating tumor cells for their nutrition [147].

Albumin based NPs have been prepared and tested as DDS in different types of cancer. Albumin nanoparticles decorated with RGD were used as DDS in the treatment of pancreas cancer. RGD was bound to the nanoparticles'surface with the aim of targeting integrin $\alpha v\beta 3$, which is expressed in pancreatic tumor cells. The nanoparticles were prepared by the desolvation-crosslinking method conjugated with RGD and loaded

with fluorescein isothiocyanate (FITC).Gemcitabine was used as the anti-cancer drug.The in vitro tests, conducted on BxPC-3 cells, showed that the presence of RGD at the surface of the nanoparticles led to a higher intracellular uptake when compared with the nanoparticles without the tripeptide[149].The nanoparticles, loaded with gemcitabine, have shown improved anti-tumor efficacy, both *in vitro* and *in vivo*.

The α-amino acids resulting from the lysosomal digestion of albumin are used by the cancer cells as a source of nitrogen and energy. There is already an injectable formulation of PTX(paclitaxel) albumin nano particles, known as Abraxane®, that has been used in the treatment of breast cancer [24;150].

4. BIOABSORBABLE SYNTHETIC NANOPOLYMERS

The aliphatic polyester poly(lactic acid) (PLA), the copolymerpoly(lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactone)(PCL) (Fig. 1) are by far the most used bioabsorbable synthetic polymers in the biomedical field [24;151].

As mentioned before, several radiopharmaceuticals have been used for both diagnosis and therapy. In order to improve the performance of radiopolymers, in particular their penetrability and specific targeting, nanotechnology has been developing micro and nano particles with the objective of improving the results of radiotherapy and the quality of diagnosis [152].

The strategies of targeting systems can be divided in: 1) passive signaling, which acts in line with the EPR effect and 2) active signaling, which use directional vectors or ligands. Passive targeting is achieved by incorporating the therapeutic agent into nanoparticle, which reaches the target organ via passive form. Drugs encapsulated in nanoparticles can passively reach the tumors through the EPR effect [153-155].

668 The methods of preparing polymer nanoparticles are generally classified in
669 methods based on the in situ polymerization of dispersed monomers (alkyl
670 cyanocrylate) or precipitation of preformed polymers (nanoprecipitation) [156]. The
671 double emulsion method is better appropriate for the nanoencapsulation of hydrophilic
672 drugs. The method consists in the preparation of a water/oil (w/o) primary emulsion by
673 sonication of a small volume of water containing the drug and an organic solvent
674 containing the polymer. This emulsion consists of the inner phase of the second
675 emulsion, also prepared by sonication, the outer phase of which is an aqueous solution
676 of the surfactant. The preparation of the nanoparticle formulations by this method
677 requires the presence of an emulsifying agent to stabilize the dispersed phase in a
678 multiple emulsion. After the establishment of a water/oil/water (a/o/a), the solvent is
679 removed by evaporation [157;158]. This method requires a high energy homogenization
680 and the particle size can be controlled by the speed and time of agitation or sonication
681 [157].
682 The development of nanoradiopharmaceuticals, provides a new paradigm for
683 both Nuclear Medicine and Radioprotection and Dosimetry emerging as a viable
684 alternative to the treatment and diagnosis of tumors [159;160]. There exist various
685 synthetic biodegradable polymers such as (poly(hydroxylbutyrate), poly anhydride
686 copolymers, poly(orthoester)s, polyphosphazenes, poly(amidoester)s, poly(cyano
687 acrylate)s and PLGA [80].
688
689 a. **Poly(lactic-*co*-glycolic acid) and Polylactic acid**
690
691 PLGA is obtained through the copolymerization of LA(or lactide) and glycolic
692 acid (GA) (or glycolide), and the properties of the copolyester can be easily tailored by

changing the relative amounts of monomers in the final copolymer. The products of degradation are existing metabolites lactic acid and glycolic acid (LA and GA, respectively) of the human body [24;161].

Due to their biodegradability, biocompatibility, and possibility for development of sustained-/controlled-/pulsatile-release and targeted delivery, PLGA is a widely used polymer. It has been approved by the United State Food and Drug Administration (FDA) for various therapeutic/diagnostic applications [162]. It should be noted that PLGA undergoes hydrolytic degradation in aqueous environment where ester linkages along with the polymer backbone are randomly hydrolyzed. The ratio LA to GA plays an important role in degradation mechanism of the PLGA. For instance, PLGA 50:50 degrades at a faster rate in comparison with PLGA 85:15 due to the higher hydrophilic GA content of the copolymer [163; 164].

Technically, PLGA NPs can be formulated by emulsification–diffusion, solvent emulsion–evaporation, interfacial deposition, or nanoprecipitation methods However, the scale-up process of PLGA NPs' formulation by means of these methods appears to be costly [165].Cisplatin and cisplatin prodrugs are broad-spectrum chemotherapeutics that have been loaded into polymeric nanoparticles, in attempts at avoiding systemic delivery of these relatively-hydrophilic small molecule drug complexes. Mitaplatin-loaded PEG-*b*-PLGA nanoparticles, stabilized with poly(vinyl alcohol) (PVA), using a double emulsion method encapsulation of mitaplatin is equivalent to the dual loading of cisplatin and DTIC (dacarbazine) for combinational therapy [167]. The resulting nanoparticles showed prolonged circulation times, reduced accumulation of Pt in the kidneys, and long-term efficacy by controlled drug release *in vivo*[167;168].

PLGA is the most used bioabsorbable synthetic polymers employed to prepare nanoparticles for cancer treatment. In 2012, Danhier et al.[172] devoted part of their

718 review article entitled "PLGA-based nanoparticles: An overview of biomedical
719 applications" to the useof PLGA nanoparticles in cancer treatment. In the lastyears,
720 PLGA-based DDSs have been developed and testedas carriers of different drugs to treat
721 different types of cancer [172-166].

722 PLGA nanoparticles prepared for the delivery of small interfering ribonucleic
723 acid (siRNA) in tumors has already been reported [170]. The *in vivo* results showed that
724 the PLGA-based DDS was effective in controlling the growth of tumor and in
725 prolonging the knockdown of the PLK1 gene, which is essential for mitosis. More
726 recently, Wang et al. [171]co-encapsulated doxorubicin (DOX) and epidermal growth
727 factor receptor (EGFR) siRNA in PLGA nanoparticles in which the angiopep-2 (ANG)
728 was conjugated .ANG is a brain-targeted peptide, and its use could bring advantages in
729 overpassing the blood brain barrier (BBB). The DDS was tested *in vitro* making use of a
730 U87MG cell line (human primary glioblastoma cell line). Co-encapsulated
731 nanoparticles were able to efficiently release the DOX and siRNA, contributing to an
732 inhibition of the cell growth, apoptosis, and EGFR silencing. The *in vivo* tests showed
733 that DDS was capable of crossing the BBB and the therapy using both EGFR siRNA
734 and DOX contributed to extend the survival time of the U87MGglioma-bearing mice.
735 Vascular endothelial growth factor receptor (VEGFR) conjugated to the surface of
736 PLGA nanoparticles encapsulating PTX. The PLGA-nanoparticles were prepared by the
737 emulsion-solvent evaporation method, and then, the VEGFR was conjugated to the
738 nanoparticles' surface. The results showed that16.6 wt.% of VEGFR was conjugated to
739 the nanoparticles surface. The anti-tumor activity of PTX encapsulated in the VEGFR-
740 PLGA nanoparticles was studied in vitro making use of 7721 human hepatocarcinoma
741 cells and A549 human lung cancer cells. The results showed that the PTX-loaded

742 VEGFR-PLGA nanoparticles have a high inhibitory activity of tumor growth when
743 compared with native PTX or with PTX-loaded PLGA-nanoparticles [172].

744 The cytotoxic effect of encapsulated gold nanoparticles in PLGA nanoparticles
745 coatedwith a lipid PEG monolayer was tested in 2D monolayers of breast cancer cells
746 (SUM-159) and 3D tumor spheroids of glioblastoma multiform cells(U87MG). The
747 overall results suggest that the encapsulation of the AuNPs in the coated PLGA
748 nanoparticles improved the photothermal ablation [62].

749 The development of biocompatible drug nanocarriers can enhance the
750 physiological stability of PTX [14–16].Moreover, 131I, was used to radiolabel the
751 PLGA-lipid nanoparticles to clearly assess their *in vivo* behavior. The results
752 demonstrate that the ^{131}I-labeled PLGA-lipid nanoparticle can be simultaneously
753 applied for targeted drug delivery and reliable tracking of drugs in vivo[173].Oncogel^{TM}
754 (ReGel^{TM}/paclitaxel) is a paclitaxel delivery system comprised of PLGA-PEG-PLGA
755 triblock copolymer (ReGel) andthe drug. It's a thermo sensitive controlled drug delivery
756 system. Oncogel can be successfully used for the site specific targeting of the tumor;
757 and also it shows synergistic effects in combination therapy [174].Encouraging results
758 inthe treatment of skin SCC have been reported inA431 cells (derived from human
759 epidermoid SCC),by using PLGA coated 5-aminolevulinic acid [175].

760 Dacarbazine (DTIC)- loaded PLAconjugated to TRAIL-receptor-2 (DR5)
761 monoclonal antibody (DTIC-NPs-DR5 mAb) provides an activetargeting DDS [176].
762 Also, cucurbitacin (Cuc)-loaded PLGA-nanoparticles can act as sustained-release
763 system for intra tumor injection [177]. A novel poly(d,l-lactide-co-glycolide) (PLGA)
764 lipid nanoparticles (PNPs) conjugate to folic acid (FA) and indocyanine green (ICG),
765 loaded with resveratrol for targeted delivery of anticancer drug and fluorescence

766 imaging. Intravenous injection of these PNP into U87 tumor-bearing mice demonstrated
767 a tumor inhibition effect [162].

768 PLA was discovered in 1932 by Carothers (at DuPont). He was only able to
769 produce a low molecular weight PLA by heating lactic acid under vacuum while
770 removing the condensed water. The problem at that time was to increase the molecular
771 weight of the products; and, finally, by ring-opening polymerization of the lactide, high-
772 molecular weight PLA was synthesized. PLA was first used in combination with
773 polyglycolicacid (PGA) as suture material and sold under the name Vicryl inthe U.S.A.
774 in 1974 [178Mehta 1996].PLA can be obtained either from the poly-condensation of
775 lactic acid (LA) or by the ring opening polymerization(ROP) of lactide. This polyester
776 can exist in four different morphological forms: poly(L-lactic acid) (PLLA),poly(D-
777 lactic acid) (PDLA), the racemic poly(D,L-lacticacid) (PDLLA), and meso-PLA. PLLA
778 and PDLA aresemi-crystalline, and PDLLA is amorphous in nature. Typically, these
779 polyesters degrade by the hydrolysis ofthe ester linkage, giving LA as the degradation
780 product[24]. In biomedical applications, PDLLA presents a faster degradation time than
781 PLLA, being more suitable for drug delivery applications [151].

782 Indocyanine green, a near-infrared fluorophore, was encapsulated into
783 proteinoid-poly(lactic acid) nanoparticles, which were used to image colon cancer
784 tumors in a LS174t colorectal cancer orthotopic mouse model. Based on the
785 overexpression of CEA by LS174t cells, the nanoparticles localized to tumor tissue and
786 generated fluorescent signal at the tumor sites. In comparison, control nanoparticles
787 without anti-CEA antibody produced no appreciable fluorescence signal, indicating the
788 enhancement of tumor targeting achieved through the use of antibodies [179].

789 Although less used than PLGA, PLA-based nanoparticles also showed to be
790 promising as anti-cancer drug DDS. Additionally, the nanoparticles were subjected to a

magnetic resonance imaging (MRI)scanning analysis, and it was shown that the nanoparticles had higher longitudinal relaxivity in water than the Mn-porphyrin, making them excellent candidates to be used in T1-weighed MRI [180].Very recently, Yang et al. developed a DDS based on PLA nanoparticles for the treatment of lung cancer metastasis. The nanoparticles encapsulating docetaxel (DTX) were prepared by the single emulsion method and a targeting peptide was conjugated on their surface. The targeting peptide, screened from lung carcinoma stem cells, showed a high specific-binding ability to pulmonary adenocarcinoma tissue. The anti-metastatic efficacy of the nanoparticles was tested in vivo making use of a nude mice model of liver metastasis. The results revealed that the peptide had a key role in the anti-metastatic efficacy of the nanoparticles [24;181].

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5. Conclusões

A micropartícula polimérica com Etoposídeo marcada com ^{99m}Tc demonstrou ser um micro-radiofármaco com potencial para ser usado no diagnóstico precoce do câncer de pulmão, no entanto, o uso de um polímero no processo de produção das micropartículas se mostrou estável e capaz de atingir o tumor em alta concentração.

Os dados de biodistribuição também demonstraram que a depuração renal é eficaz e mostrou captação insignificante pelo cérebro. Os resultados de imagem SPECT corrobora a biodistribuição e também mostrou a possibilidade de uso deste micro-radiofármaco como agente de imagem.

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