UNIVERSIDADE D
COIMBRA

Carolina Rodrigues Mesquita

Relatório de Estágio e Monografia intitulada "NSAIDS-loaded nanocarriers for next generation cancer treatment" referentes à Unidade Curricular "Estágio", sob a orientação da Dra. Maria do Carmo Moço e do Professor Doutor Francisco Veiga, apresentados à Faculdade de Farmácia da Universidade de Coimbra para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas

Setembro de 2022

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Setembro 2022

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Coimbra, 9 de setembro de 2022

Carolina Rodrigues Mesquita

(Carolina Rodrigues Mesquita)

"I don't even have a 'pla"'

Phoebe Buffay

AGRADECIMENTOS

A Coimbra, que me ensinou, durante estes 5 anos, o verdadeiro significado de ser estudante. És a canção que nunca esquecerei.

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PARTE I

Relatório de Estágio em Farmácia Comunitária

Farmácia Moço

LISTA DE ABREVIATURAS

ARS – Administração Regional de Saúde

DGS – Direção-Geral de Saúde

FFUC – Faculdade de Farmácia da Universidade de Coimbra

MICF – Mestrado Integrado em Ciências Farmacêuticas

MNSRM – Medicamento Não Sujeito a Receita Médica

MSRM – Medicamento Sujeito a Receita Médica

SARS-CoV-2 – *Severe Acute Respiratory Syndrome Coronavirus-2*

SWOT – *Strengths, Weaknesses, Opportunities, Threats*

1. INTRODUÇÃO

O farmacêutico é por definição o especialista do medicamento, mas além disso, é também um agente de saúde pública e na maior parte das situações, o primeiro contacto do paciente com um profissional de saúde. Em Farmácia Comunitária, grande parte do papel desta profissão é o contacto próximo com o público, permitindo a existência de confiança mútua entre profissional e utente, a qual é edificada pelas competências científicas e técnicas dos farmacêuticos. A qualidade da atividade baseia-se em valores como a integridade, a transparência e o empenho, tendo como objetivo assegurar e promover o bem-estar e saúde do doente (Pita e Bell, 2016).

Nos dias que correm, a intervenção do farmacêutico e a sua atividade profissional englobam cada vez mais vertentes, exigindo destes elevados níveis de rigor e grande responsabilidade (Ordem dos Farmacêuticos, 2021). Nas suas funções denotam-se: a dispensa de medicamentos sujeitos a receita médica (MSRMs) e de medicamentos não sujeitos a receita médica (MNSRMs), dispositivos médicos, suplementos alimentares, produtos cosméticos, medicamentos veterinários, entre outros; Medição e avaliação de certos parâmetros bioquímicos, fisiológicos e físicos; Revisão, avaliação e otimização da terapêutica dos utentes; Administração de Injetáveis; Além do dever ético e profissional de agente de saúde pública na comunidade onde se encontra integrado (INFARMED, 2021).

O Estágio Curricular em Farmácia Comunitária é uma das etapas do plano de estudos do Mestrado Integrado em Ciências Farmacêuticas (MICF) da Faculdade de Farmácia da Universidade de Coimbra (FFUC). Este estágio permite a consolidação de toda a aprendizagem teórica adquirida ao longo dos cinco anos de formação, ligando estes conhecimentos à atividade profissional e dando oportunidade aos alunos de ter um contacto com um dos muitos contextos profissionais para os quais o Mestrado Integrado nos prepara, sendo por isso uma etapa imprescindível no percurso aluno, enquanto futuro farmacêutico.

O meu Estágio Curricular foi realizado na Farmácia Moço (FM), escolha que se baseou na sua localização, na afluência e diversidade de utentes e na sua reputação como farmácia de referência na comunidade da cidade de Coimbra. Estagiei sob orientação da Diretora Técnica e também proprietária da farmácia, Dra. Maria do Carmo Moço, entre abril e julho de 2022, perfazendo um total de 648 horas.

Este relatório foi feito através de uma análise SWOT (*Strengths, Weaknesses, Opportunities, Threats*), tendo como objetivo uma apreciação crítica desta etapa de aprendizagem e de consolidação dos conhecimentos teóricos na atividade profissional.

2. FARMÁCIA MOÇO

A Farmácia Moço está em funcionamento há cerca de trinta anos, começando em Almalaguês, uma aldeia do concelho de Coimbra, tendo, em 2012, transferido as instalações para a Avenida Fernando Namora, fazendo parte da freguesia de Santo António dos Olivais, Coimbra. contudo continuou a dar apoio à população através de entregas domiciliárias e mantendo nas mesmas instalações a parafarmácia "Farmamoço". É propriedade da Dra. Maria do Carmo Moço, que desempenha as funções de Diretora Técnica, desde 1991.

A entrada da farmácia, apesar de não ser ao nível do passeio exterior, encontra-se equipada com uma rampa, permitindo o acesso de utentes com mobilidade reduzida. O local de atendimento apresenta cinco balcões de atendimento, sendo que 4 estão alinhados e o quinto encontra-se separado dos restantes, permitindo assim dar apoio em atendimentos mais especializados. Na área de atendimento encontram-se expostos nos diferentes lineares produtos de dermocosmética, suplementos alimentares, puericultura, ortopedia, assim como os produtos de veterinária e MNSRM que se encontram nos lineares atrás dos balcões. Tanto os produtos de veterinária não sujeitos a receita médica como os MNSRM estão dispostos de forma que o utente não tenha fácil acesso aos mesmos, permitindo sempre um aconselhamento farmacêutico antes da dispensa.

A Farmácia Moço é composta por diferentes áreas que se dividem entre dois pisos, organizadas segundo a deliberação 2473/2007, de 28 de novembro (Ministério da Saúde, 2007). No piso 0 existe uma sala de atendimento ao público, um laboratório para preparação de manipulados, dois gabinetes de atendimento personalizado, que permitem a realização de vários serviços onde se incluem a medição de alguns parâmetros bioquímicos assim como consultas de nutrição, atendimentos mais personalizados ou outras dinamizações realizadas por diversas marcas, como formações internas e rastreios, assim como testes à COVID 19, instalações sanitárias e gabinete da direção técnica1. No piso -1 localiza-se a zona de receção de encomendas, uma divisão com acesso ao exterior da farmácia, assim como a zona de armazém. Esta zona de armazém permite o acondicionamento de grande parte do *stock* de medicamentos e outros produtos nas condições necessárias para a sua conservação, devidamente organizados alfabeticamente e por categoria.

O horário de funcionamento da Farmácia Moço é continuo, de segunda a sexta-feira, das 9h às 21h30 e sábado, das 9h às 20h. Em conformidade com a Administração Regional de Saúde (ARS) do Centro, a Farmácia Moço efetua serviço permanente de vinte em vinte dias, mantendo-se em expediente desde a hora de abertura até à hora de fecho do dia seguinte.

Nesses dias a porta é fechada à 00h, sendo os atendimentos posteriores realizados através do postigo, localizado numa das portas, até às 9h do dia seguinte.

3. ANÁLISE SWOT

A matriz SWOT é uma ferramenta de gestão que permite estabelecer objetivos assim como desenvolver estratégias, resultando na potenciação da área na qual é aplicada, sendo estruturada em duas dimensões: a interna, na qual são avaliados os pontos fortes (*Strengths*) e pontos fracos (*Weaknesses*); e a externa, na qual são avaliadas as oportunidades (*Opportunities*) e as ameaças (*Threats*) (Silber *et al.*, 2010).

3.1. Pontos Fortes (*Strengths*)

3.1.1. Localização e contexto da farmácia

A Farmácia Moço encontra-se numa ampla zona habitacional, na beira de uma das principais artérias de trânsito da cidade de Coimbra, proporcionando-se assim uma vasta afluência de utentes. A sua localização chama à atenção dos condutores, que muitas vezes vêm de diferentes pontos para consultas ou visitas no Hospital da Universidade de Coimbra. A farmácia apresenta parque de estacionamento, o que se torna apelativo para os utentes. Uma vez que o parque de estacionamento é amplo, o acesso para transportes especiais de doentes é facilitado, sendo isto uma mais-valia para a farmácia. Desta forma a farmácia acaba por ter clientes fidelizados não só da zona, mas também dos arredores de Coimbra.

3.1.2. Utentes

A carteira de utentes que frequenta a Farmácia Moço é ampla e diversificada, devendo-se isso tanto à localização atual como a prévia localização. Desde utentes de passagem, dada a proximidade de uma das principais artérias de trânsito da cidade de Coimbra, até utentes que se encontram fidelizados à farmácia desde a sua fundação, em Almalaguês, ou utentes fidelizados apenas desde a sua transferência para a localização atual, sendo por isso talvez uma das farmácias da cidade com maior fluxo de clientes.

Além da vantagem a nível económico que esta diversidade e grande número de utentes que apresenta, é também uma vantagem a nível científico e profissional, pois pela diversidade de faixas etárias, condições socioeconómicas, diferentes patologias e históricos farmacológicos, permite o contacto constante com diferentes situações, enriquecendo assim constantemente o conhecimento profissional e tendo sido uma grande mais-valia na minha experiência como estagiária. Esta heterogeneidade de utentes deu-me a possibilidade de

adaptar os métodos de comunicação de acordo com cada utente, tornando cada atendimento único e distinto e enriquecendo assim a minha capacidade do ponto de vista profissional.

Na Farmácia Moço há também muitos utentes que procuram produtos para situações mais específicas e que exigem um aconselhamento bastante diferente do habitual, por exemplo, utentes com necessidades de dispositivos médicos como meias elásticas.

3.1.3. Equipa Técnica

A equipa profissional da Farmácia Moço é jovem, dinâmica e altamente qualificada, sendo constituída por cinco farmacêuticos (Dra. Ana Fonseca, Dra. Inês Lucas, Dra. Jéssica Lopes e Dr. João Aveiro) inclusive a Diretora Técnica, Dra. Maria do Carmo, e três Técnicos de Farmácia (Dr. Daniel Silva, Dra. Márcia Bastos e Dr. Pedro Silva), apesar de, em julho, a Farmácia ter deixado de contar com a presença do Dr. Pedro. Destaca-se pelo seu elevado profissionalismo, simpatia, cooperação e constante criação de relações com os utentes, sendo evidente a relação interpessoal que muitos dos utentes regulares têm com a equipa da farmácia. Também eu tive oportunidade de ser acolhida por esta equipa, sendo que desde o primeiro dia fui integrada na equipa, com um nível constante de ensinamentos e um aumento gradual de confiança e cumplicidade com toda a equipa, dando-me assim a oportunidade e confiança de questionar, aprender, melhorar e crescer, quer a nível profissional, quer a nível pessoal.

O sucesso com que sinto que concluí esta etapa deve-se também à equipa da farmácia e a relação que durante este tempo se estabeleceu. Além de todo o conhecimento teórico e técnico que me foi transmitido, adquiri também valores de atenção, rigor e profissionalismo.

Foi a excelência desta equipa que se preza por valores de exigência, qualidade de serviço e simpatia que todos os dias me motivou para uma aprendizagem e melhoria contínua, proporcionando-me assim uma desafiante, mas enriquecedora experiência de estágio.

3.1.4. Plano de Estágio

A Farmácia Moço e toda a sua equipa primam pela sua organização, virtude que também pude constatar na planificação do meu estágio. O estágio curricular pode ser inicialmente intimidante, dada a obvia diferença entre esta etapa e o restante percurso curricular, as várias tarefas a cumprir e diferentes etapas de trabalho por onde passamos, além de ser muitas vezes o primeiro contacto real com a atividade profissional. No primeiro dia a foram-me apresentadas, pela Dra. Maria do Carmo, as instalações, a equipa, os principais objetivos do estágio e os principais valores e missões da farmácia.

A primeira etapa do estágio constituiu-se principalmente por trabalho de *backoffice,* sendo essencialmente a receção e organização de encomendas e o devido armazenamento dos produtos rececionados. Esta fase é de alguma importância pois facilita o conhecimento do circuito dos produtos desde o momento da sua chegada à farmácia, a logística de funcionamento desta e o reconhecimento dos locais de armazenamento dos produtos, bem como proporciona a familiarização com a grande variedade de produtos presentes na farmácia. Além disto, este trabalho de *backoffice* permite também a ambientação ao sistema informático em uso pela farmácia, o Sifarma2000®. Com o desenvolvimento destas apetências, outras tarefas importantes na gestão de *stocks* foram-me sendo delegadas, nomeadamente a gestão e organização de reservas, a arrumação do armazém, gavetas da zona de atendimento e organização de lineares.

No seguimento desta primeira fase, em momentos de menor atividade de *backoffice*, tive a oportunidade de acompanhar membros da equipa técnica durante os seus atendimentos, tendo assim o primeiro contacto real com receituário manual e guias de tratamento, receitas sem papel (por SMS, mail ou outro formato eletrónico), com o Módulo de Atendimento e com a medição de valores de parâmetros físicos e bioquímicos e respetiva interpretação dos mesmos.

A última fase do estágio consistiu na realização de atendimento ao público, inicialmente sob a supervisão e acompanhamento de um membro da equipa técnica e, gradualmente, de forma mais autónoma, à medida que as minhas capacidades de comunicação e de dinâmica de atendimento e os meus conhecimentos teóricos e práticos se consolidavam. De notar o excelente apoio que recebi de toda a equipa durante esta progressão entre fases, sendo-me possível ter uma evolução contínua, quer a nível de conhecimentos, quer a nível de confiança, segurança e autonomia.

3.1.5. Automatização da farmácia

A Farmácia Moço prima pela modernização das instalações e atendimentos, sendo este um aspeto de importância crescente na atualidade. Alguns exemplos disso a adesão ao Novo Módulo de atendimento do Sifarma2000®, a existência do sistema *Safepay*™, e uma máquina para a preparação individualizada da medicação.

O *SafePay*™ é um equipamento utilizado por todos os colaboradores nos atendimentos para a realização dos pagamentos das vendas em dinheiro, registando todos os movimentos monetários realizados. Além disso, esta tecnologia minimiza o erro humano, uma vez que calcula e retorna automaticamente o troco de cada pagamento, tornando assim o processo mais célere e tornando o armazenamento do dinheiro mais seguro.

A preparação individualizada da medicação tem essencialmente a função de evitar os erros de medicação em doentes polimedicados, com pouca autonomia e institucionalizados.

3.1.6. Mercado de Cosméticos

Na sua definição, um produto cosmético é toda a "*substância ou mistura destinada a ser posta em contacto com as partes externas do corpo humano (epiderme, sistemas piloso e capilar, unhas, lábios e órgãos genitais externos) ou com os dentes e as mucosas bucais, tendo em vista, exclusiva ou principalmente, limpá-los, perfumá-los, modificar-lhes o aspeto, protege-los, mantê-los em bom estado ou corrigir os odores corporais*" (União Europeia, 2010).

O mercado dos produtos cosméticos está cada vez mais atrativo, quer pela crescente procura por parte dos utentes, quer pela crescente aposta das marcas nestes produtos, fazendo aparecer uma grande variedade de produtos e preços cada vez mais competitivos, sendo crucial a adaptação da farmácia e do farmacêutico a estas mudanças.

A Farmácia Moço possuí uma diversa gama de marcas no que toca à dermofarmácia e cosmética, desde *Soha*®, *Phyto*®, *La Roche Posay*®, *Bioderma*®, *Skinceuticals*®, *Matiderm*® e *SkinPerfection*®. Além da diversidade de marcas e produtos, o estreito contacto entre a e equipa da farmácia e os representantes das diferentes marcas que visitam a farmácia regularmente e que proporcionam à equipa diversas formações sobre os seus produtos, permitiu-me e permite à equipa manter uma constante atualização dos conhecimentos, podendo assim proporcionar o melhor aconselhamento possível aos utentes.

Nesta categoria de produtos, que já por si apresenta uma enorme diversidade, é onde se denota nitidamente a heterogeneidade de utentes, possibilitando assim o meu contacto com diferentes soluções para as enumeras necessidades dos utentes, individualizando cada atendimento.

Somando ao conhecimento da área que me foi sendo transmitido pela equipa da farmácia, todo a informação divulgada pelas diferentes representantes das diversas marcas, consegui melhorar e consolidar o meu conhecimento da área, tornando-me assim confiante no atendimento e aconselhamento ao público.

3.1.7 Domicílios e colaboração com o Lar e Centro de Dia de Almalaguês

A Farmácia Moço continua a auxiliar os utentes do lar e Centro de dia de Almalaguês o que facilita as tarefas dos funcionários do lar e dos familiares dos utentes, através da entrega domiciliária dos medicamentos. Todos utentes que assim o desejarem, poderão ter a sua medicação entregue em casa, o que se tornou particularmente útil em tempo de pandemia.

As preparações das entregas, no início do estágio, permitiram-me desenvolver competências e aptidões, principalmente no que diz respeito ao sistema informático Sifarma2000®, que tornaram o meu processo de integração ao balcão mais simples, já que o que acontece nestes casos é uma "simulação" do atendimento, sem a presença física do utente. Consequentemente, quando iniciei o atendimento ao balcão, rapidamente me adaptei, sentindo-me bastante confortável e com confiança para realizar um atendimento com o nível elevado de qualidade que é exigido na Farmácia Moço.

3.1.8 Preparação de Medicamentos Manipulados

O medicamento manipulado é uma fórmula oficinal ou magistral com ajuste terapêutico para um determinado doente, numa determinada situação. São um tipo muito específico de medicamentos que são preparados no laboratório da própria farmácia, sendo da responsabilidade do farmacêutico, para além da sua preparação, o seu acondicionamento, rotulagem e controlo de qualidade. O Decreto-Lei n.º 95/2004, de 22 de abril (Ministério da Saúde, 2004), regula a prescrição e preparação de medicamentos manipulados.

Para a preparação de manipulados é preciso preencher a respetiva ficha de preparação onde são registadas as matérias-primas utilizadas, com respetivo lote, fornecedor e a quantidade utilizada, os processos de manipulação, controlo de qualidade, matérias utilizadas, condições de conservação e prazo da sua utilização. São ainda registados o nome do doente, morada e o nome do médico prescritor. Esta ficha, juntamente com a cópia da receita medica e rótulo é arquivada por um período mínimo de três anos. O preço de venda dos manipulados é calculado com base em fórmula legislada, tendo assim em conta os materiais utilizados e a quantidade utilizada (Ministério da Saúde, 2004).

Considero que o contacto com esta atividade muito importante, pois é essencial que o farmacêutico se encontre apto a realizar todas as tarefas comuns da farmácia comunitária.

3.2. Pontos Fracos (*Weaknesses*)

3.2.1. Preparação para o atendimento ao público

O plano de estudos do Mestrado Integrado em Ciências Farmacêuticas na Universidade de Coimbra é uma referência nacional na área e destaca-se pela excecional preparação que confere, a nível teórico, aos seus estudantes. Apesar de em certas áreas, como na Farmacologia, em que a formação ao logo do MICF é extremamente completa no que diz respeito ao medicamento, e não obstante a imensa importância de todo este conhecimento, o papel profissional do farmacêutico vai muito além do âmbito do medicamento, devendo este ser capaz de responder a questões relacionadas com outras áreas, como puericultura,

dispositivos médicos, produtos de uso veterinário, entre outros, em que o contacto com estas ao longo do percurso académico não tem tanto destaque. Além das capacidades teóricas, o papel do farmacêutico pressupões também capacidades sociais, no contacto direto com a imensa variedade de pessoas que afluem à farmácia, sendo também esse um dos grandes desafios desta etapa.

No ato do atendimento ao público, a dispensa dos medicamentos inscritos na receita não é a única responsabilidade do profissional, mas também o devido aconselhamento. A fase mais entusiasmante, mas ao mesmo tempo desafiante deste estágio foi, sem sombra de dúvida, a fase de atendimento. Inicialmente, a inexperiência e algum nervosismo característico afetaram a minha confiança ao balcão, sendo de notar por vezes a não adesão de certos utentes ao atendimento por parte de um elemento novo na equipa, com o papel de estagiária. Com o passar dos dias e suporte da equipa, consegui melhorar as capacidades necessárias, conquistando até a confiança pessoal de parte dos utentes.

Senti-me sempre apoiada pela equipa da Farmácia Moço, que nunca hesitou a auxiliar-me num momento de dúvida ou simplesmente menos confiança, transmitindo sempre os seus conhecimentos de forma a poder consolidar os meus. Além da ajuda nos casos reais com que me deparei, os elementos da equipa estiveram sempre prontos a partilhar diferentes casos e experiências, preparando-me o melhor possível para qualquer situação com que me pudesse deparar num atendimento. Todos os ensinamentos foram sem dúvida cruciais para melhorar o meu método de trabalho, tornando assim os meus atendimentos mais completos, confiantes, competentes e céleres possíveis.

3.2.3. Áreas de produtos mais particulares

Algumas áreas mais particulares como produtos de puericultura leve, destinados ao aumento do conforto e desenvolvimento do recém-nascido, como chupetas, biberões, fraldas, papas e leites, áreas em que a Farmácia Moço dispõe de uma grande variedade de produtos, por não ter tido grande contacto com essas áreas ao longo do percurso académico, sempre me despontaram alguma insegurança nos atendimentos, que foi prontamente colmatada pela ajuda dos elementos da equipa técnica da farmácia.

Muitos dos medicamentos de uso veterinários vêm por prescrição médica ou por aconselhamento do médico veterinário. Contudo, a farmácia dispõe de um serviço telefónica de aconselhamento veterinário. Através deste serviço podemos tirar algumas dúvidas com médicos veterinários de forma a tornar o nosso aconselhamento veterinário mais completo.

3.2.2. Denominação Comum Internacional (DCI) versus Nome Comercial

A grande diversidade de princípios ativos existentes no mercado e a existência de, muito recorrentemente, diversos nomes comerciais para cada um deles, torna complicada a associação entre o nome comercial e o princípio ativo. Esta dificuldade foi evidente no início do estágio, contudo, com o tempo e a experiência, foi possível uma melhor adaptação neste contexto, apesar de, ocasionalmente, mesmo na fase final do estágio ter algumas dúvidas na realização desta associação.

3.3. Oportunidades (*Opportunities*)

3.3.1. Programa VALORMED®

A Farmácia Moço faz parte da rede de farmácias que participa no Programa VALORMED®, um programa sem fins lucrativos, responsável pela gestão de medicamentos fora de uso e/ou de validade e todos os resíduos das respetivas embalagens vazias, garantindo o sua recolha e tratamento correto e seguro. Estes resíduos são armazenados em contentores específicos que, uma vez cheios, são fechados, pesados e registados para posterior recolha (VALORMED, 2022).

É realmente de grande importância investir na consciencialização da população em relação à reciclagem dos medicamentos, um passo inevitável para preservar o ambiente e assegurar a saúde pública. Foi com enorme satisfação que verifiquei que muitos dos utentes fidelizados à Farmácia Moço já regularmente trazem as embalagens vazias e/ou fora de validade à farmácia para a reciclagem e que a mensagem passada por toda a equipa aos novos utentes também se fazia ouvir, havendo por vezes pessoas que apenas se dirigiam à farmácia com o objetivo de entregar essas embalagens, sendo por vezes necessário o uso de novos contentores num mesmo dia.

3.3.2. Horário Alargado

Como já foi referido antes, a Farmácia Moço encontra-se em funcionamento das 9h da manhã até às 21h30, tendo assim um expediente de mais de doze horas. Ao longo do meu estágio foi-me possível experienciar por diversas vezes uma saída nesse horário mais tardio, tendo assim por vezes contacto com um ambiente de trabalho com um fluxo de utentes bastante mais reduzido, o que possibilitava um aconselhamento mais pormenorizado e construir um ambiente de maior confiança e conforto. Era também nestes períodos mais calmos que tinha maior oportunidade de esclarecer dúvidas e melhorar os meus conhecimentos com os membros da equipa da farmácia e finalizar tarefas não concluídas durante o dia.

3.3.3. Sistemas informáticos

Estando num período de transição entre sistemas informáticos, substituindo o Sifarma 2000® pelo Novo Sifarma. Das várias funcionalidades do Novo Sifarma o Módulo de Atendimento é praticamente a única que se encontra completa (Glintt, 2022). A Farmácia Moço utiliza ambos os sistemas, sendo que o Novo Módulo de Atendimento é quase exclusivamente usado para os atendimentos. Assim, tive a oportunidade de conhecer de raiz ambos os sistemas, uma vez que esta etapa de estágio foi o meu primeiro contacto real com ambas as versões.

3.3.4. Forrmações

Durante o estágio foi-me dada a oportunidade de aprofundar os meus conhecimentos nas mais diversas áreas. Tive então a possibilidade de participar em diversas ações de formação, colmatando, desta forma, algumas lacunas do meu conhecimento em produtos de venda livre existentes na farmácia.

Foi possível adotar novas visões e aperfeiçoar as indicações a dar aos utentes da farmácia na aquisição desses produtos, em muitos dos quais, no início do estágio, tinha dúvidas nos aconselhamentos farmacêuticos adequados. Estas formações foram bastante úteis para conhecer a gama de produtos comercializada pelas marcas, os seus ingredientes-chave, bem como o público-alvo a quem os aconselhar. Destaco desta forma as formações dos Laboratórios Cantabria®, Sanofi®, Aboca®, Soha® e SkinPerfection®.

3.4. Ameaças (*Threats*)

3.4.1. Medicamentos Esgotados

Uma das grandes problemáticas com que me deparei no estágio foi a questão dos medicamentos esgotados. O meu primeiro contacto com esta questão deu-se durante a receção de encomendas, onde várias vezes me deparava com diversas falhas de medicamentos esgotados ou rateados. Depois de iniciar a realização de atendimentos, esta questão tornou-se ainda mais real, uma vez que me deparei com utentes impossibilitados de ter acesso aos medicamentos necessários à manutenção das suas terapêuticas, quer por falta de opções ou por insistência dos mesmo em não trocar pelas opções disponíveis (genéricos ou uma troca de laboratório), levando isso à necessidade de um atendimento mais cuidado e sensível, sendo por vezes difícil explicar aos utentes que estas falhas abruptas de *stocks* eram questões alheias à farmácia.

Durante este período de estágio, esta dificuldade fez-se notar, particularmente, com Zarator® nas dosagens de 20 e 40mg, Zoloft® assim como Ozempic®.

A equipa técnica da Farmácia Moço, perante este obstáculo, adotou uma estratégia de reservas para estes medicamentos, organizando listas por ordem cronológica de pedidos destes medicamentos esgotados ou rateados, com o nome e contacto do utente, mediante apresentação de prescrição médica, de forma a distribuir da melhor maneira possível, as pequenas quantidades que por vezes se conseguiam arranjar.

Estas falhas, além de prejudicar os utentes, obrigados a suspender ou adiar o início das suas terapêuticas, prejudica também a farmácia, uma vez que esta, por motivos alheios, se vê numa posição de incapacidade de cumprir com as espectativas e necessidades dos seus utentes.

3.4.2. Mercado Competitivo

Apesar da sua localização de excelência, a Farmácia Moço encontra-se numa zona onde existem bastantes outras farmácias. Além disso, as farmácias portuguesas na sua generalidade, estão sujeitas a um elevado nível de concorrência no que toca a produtos de venda não exclusiva em farmácias, como o caso dos MNSRM e produtos de saúde e bem-estar, como suplementos alimentares. Os outros locais de venda de MNSRM, nomeadamente as lojas *online*, disponibilizam uma facilidade desmedida na obtenção destes produtos, constituindo assim uma grande ameaça à profissão farmacêutica e ao próprio conceito do medicamento, podendo torná-lo banal.

Ao longo do meu período de estágio várias vezes me deparei com utentes que não compravam MNSRM ou outros produtos de venda não exclusiva na farmácia devido constante à comparação de preços. Nesta guerra de preços a farmácia muitas vezes perdia, não propriamente para lojas físicas, mas essencialmente para lojas *online*, que muitas vezes conseguem ter um preço mais reduzido. Intrigou-me a variedade de utentes que demonstravam interesse em certos produtos, procurando aconselhamento sobre os mesmos, podendo assim adquirir conhecimentos que só são possíveis vindos de profissionais qualificados, com a intenção de à posteriori adquirir esses mesmos produtos numa superfície comercial ou numa loja *online*. É de extrema importância que a comunidade em geral esteja consciente de que, apesar dos preços por vezes mais acessíveis, essas lojas não dispõem de profissionais suficientemente qualificados para executar um atendimento e aconselhamento personalizado, seguro, responsável e adequado a cada caso individual.

É fulcral reconhecer o caráter insubstituível do farmacêutico e a sua notória qualificação, sendo fundamental que este profissional invista num aconselhamento completo e numa sensação por parte do utente de atendimento individualizado, de forma a diferenciar-se na promoção da saúde e da segurança da comunidade.

3.4.3. Pandemia COVID-19

A totalidade do meu estágio curricular decorreu num período ainda marcado pela realidade da adaptação à COVID-19. Apesar de se ter dado numa altura em que a situação pandémica se encontrava mais calma, as farmácias e espaços de saúde ainda se encontravam abrangidas por todas as normas de segurança e recomendações da Direção-Geral de Saúde (DGS), que sempre foram seguidas rigorosamente, levando por vezes a algumas alterações de logística na farmácia.

Cada posto de atendimento encontrava-se protegido por uma barreira de acrílico, oque por vezes criava dificuldades na comunicação com o utente, em particular os utentes mais idosos. Além de sentir uma relação mais afastada do utente, pela presença de uma barreira física, houve vários momentos de confusão na comunicação devidos a medicamentos *sound-alike* como, por exemplo, *Aspira*®C e "Aspirina 100" (*Aspirina*® 100mg).

Outro aspeto delicado e fatigante com que me deparei, enquanto futura profissional de saúde, foi a desinformação ou descredibilização de alguns utentes perante o SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus*-2). Dentro das minhas capacidades e de acordo com todo o conhecimento científico disponível, exerci da melhor forma que me foi possível a minha função de agente de saúde pública e tentei elucidar utentes sobre tópicos que estes não tinham clarificados na sua mente.

O SARS-CoV-2 transformou a nossa realidade e trouxe para as nossas vidas um novo conceito de "normal". É dever profissional e ético dos profissionais de saúde, sobretudo dos farmacêuticos dada a sua posição privilegiada de contacto tão próximo com a comunidade, educar e esclarecer a população, especialmente numa altura em que o acesso a muita "desinformação" se encontra tão facilitado pelo acesso à *internet* e redes sociais.

3.4.4. Erros no *Stock*

Nos casos em que o *stock* de um produto está errado, o sistema informático pode indicar a existência do mesmo quando na realidade o *stock* físico é nulo. Estes erros constituem uma ameaça nos produtos com menor *stock,* podendo impedir a farmácia de assegurar uma disponibilidade imediata de determinado item.

Esta situação pode também ameaçar a fidelização dos utentes, uma vez que face à informação que consta no Sifarma2000®, confirmamos a existência do produto e no momento de procedermos à sua recolha, perdemos algum tempo à procura do mesmo até concluirmos

a sua inexistência, o que se torna bastante desagradável para o utente que após o tempo de espera, sai sem o produto.

3.4.5. Tempo de Espera

Em determinados momentos do dia, a afluência de utentes à farmácia é maior, coincidindo normalmente com os horários pós-laborais, mais precisamente entre as 17h e as 20h. Nestas ocasiões, a fim de reduzir o tempo de espera e evitar uma acumulação excessiva de utentes na sala de atendimento, o processo de dispensa de medicamentos tem de ser acelerado, diminuindo assim a disponibilidade necessária que alguns utentes anseiam e solicitam. Após um período de espera mais demorado, o próprio utente encontra-se agitado e impaciente, sendo esta atitude uma das maiores barreiras à boa atuação do farmacêutico.

4. CASOS PRÁTICOS

CASO I

Uma jovem, com cerca de 25 anos, dirige-se à Farmácia Moço queixando-se que lhe tinham aparecido nas mãos várias borbulhas pequenas que lhe causavam muita comichão. Disse que era cabeleireira e que, de tempos a tempos, tinha este tipo de reação. Já tinha tomado Cetix®, aconselhado noutra farmácia, mas não tinha sentido diferença e que agora estava a tomar Aerius®, contudo sentia que necessitava algo mais.

Aconselhei-lhe o uso de *Pandermil*® (creme de Hidrocortisona 10mg/g), questionando-a antes se está grávida e/ou em amamentação e sobre possíveis alergias aos componentes do creme, às quais me responde que não. Informo-a que deve aplicar localmente pequenas quantidades de creme 2 a 3 vezes por dia, numa duração máxima de 7 dias (Laboratório Edol - Produtos Farmacêuticos S.A, 2019), sendo que, se piorar ou não vir melhorias deve dirigir-se ao seu médico. Uma vez que dado à profissão entra em contacto direto com vários tipos de produtos, aconselhei-a também a usar luvas, de preferência com pó.

CASO II

Uma senhora dirige-se à Farmácia Moço à procura de suplementação nutricional oral para o pai, um doente oncológico, dizendo que ele tem bastante dificuldade em deglutir fazendo com que ingerisse pouca quantidade de alimentos. O senhor estava bastante emagrecido e a filha queria um suplemento para completar as refeições de forma a aumentar o aporte nutricional ao longo do dia.

Questionei se o utente tinha mais alguma patologia que fosse relevante ou se se engasgava com facilidade. Respondeu-me que o pai era diabético, mas que estava controlado, mas que realmente engasgava-se algumas vezes.

Aconselhei-lhe Fresubin® DB Créme que é um produto direcionado para diabéticos numa apresentação de creme, sendo mais seguro para um utente com disfagia. Informei que uma vez está a ser utilizado como suplementação, devem ser tomadas 2-3 embalagens ao dia, tendo também em atenção as necessidades do senhor (Fresenius Kabi Pharma, 2021). No entanto se não fosse possível ingerir a quantidade recomendada dei a informação para ingerir o que fosse possível, mantendo o restante no frigorífico por um período máximo de 24h. Como o utente apresentava disfagia aconselhei também um espessante à base de goma xantana e resistente à amilase salivar, para colocar na sopa ou na água de forma a evitar que o utente se engasgasse (Ikeda *et al.*, 2021).

CASO III

Um senhor, com cerca de 50 anos, dirige-se à Farmácia Moço à procura de aconselhamento farmacêutico. Refere há 4 dias que não consegue ir à casa de banho, o que é estranho, atendendo à sua frequência normal, diária, de dejeções. Quando questionado, nega outros problemas de saúde ou estar a fazer qualquer tipo de medicação.

Comecei por aconselhar a adoção de algumas medidas preventivas, de natureza não farmacológica como a ingestão de 1 L a 2 L de água/dia e de alimentos ricos em fibras (frutas, vegetais, cereais integrais, etc.) assim como a prática regular de exercício físico, por exemplo. Aconselhei, depois, Dulcolax® (bisacodilo) 5 mg, comprimido revestido, um laxante de contacto. Indiquei ao senhor que tomasse 1 comprimido ao deitar, de forma que o efeito do mesmo se produzisse na manhã seguinte (INFARMED, 2014). Adicionalmente, adverti o senhor para a "agressividade" do laxante dispensado, referindo que este deve ser tomado apenas em situações pontuais, como era o caso, e não de forma recorrente.

CASO IV

Uma senhora dirige-se à Farmácia Moço em busca de aconselhamento na escolha de protetores solares para o rosto.

Na escolha de possíveis sugestões, tive em conta diversos fatores, nomeadamente o tipo de pele e o seu fototipo. Diz-me que tem a pele sensível e que qualquer tipo de fragrância no protetor lhe causa irritação cutânea, pelo lhe é difícil encontrar um protetor que seja compatível com a sua pele. Desta forma, sugeri o protetor *Heliocare 360º Mineral Tolerance Fluid* com SPF 50, que está adaptado para peles sensíveis ou atópicas. Adicionalmente, reforcei

as medidas a adotar para uma exposição solar segura: não expor demasiado tempo a pele ao sol, aplicar o protetor pelo menos trinta minutos antes da exposição, fazer reaplicações regulares e evitar as horas de maior radiação.

CASO V

Um jovem dirige-se à Farmácia Moço queixando-se de ter os olhos "muito vermelhos" nos últimos dias. Após algumas questões, refere que os sintomas afetam os dois olhos e que, além da vermelhidão, sente algum ardor e os olhos cansados, sobretudo ao final do dia. Não apresenta sintomas nasais concomitantes ou secreções oculares, nem sofre de condições alérgicas. Refere, ainda, que não usa óculos ou lentes de contacto. Acrescenta que, por se encontrar em época de exames, tem passado muito tempo ao computador.

Conclui que, provavelmente, se tratava apenas de um caso de secura ocular. Aconselhei assim Hyabak® (hialuronato de sódio 0,15%), um hidratante e lubrificante ocular. Expliquei que poderia aplicar 1 gota em cada olho, várias vezes ao dia, no canto do saco lacrimal inferior, puxando ligeiramente a pálpebra inferior para baixo e dirigindo o olhar para cima (Laboratoires Théa, 2013). Informei, também, que, antes de proceder à aplicação, deveria lavar bem as mãos e evitar tocar com o conta-gotas nas pálpebras ou no olho. Alertei, ainda, para a importância de descansar os olhos enquanto trabalha no computador, aconselhando desviar o olhar do computador com regularidade, focando-o em objetos mais distantes.

5. CONSIDERAÇÕES FINAIS

O meu estágio curricular na Farmácia Moço foi o culminar do meu percurso académico e foi essencial para consolidar todo o conhecimento teórico e prático que adquiri ao longo destes cinco anos do MICF, sendo também crucial para reavaliar algumas das ideias pré-concebidas que tinha sobre farmácia comunitária. Desde o início soube que o papel do farmacêutico não se limita à dispensa de receitas médicas, mas ao longo desta etapa pude perceber o grande impacto que tem o contributo do farmacêutico na vida dos utentes.

Durante estes três meses pude desenvolver valências a nível pessoal, social e profissional, graças à incrível equipa da Farmácia Moço que desde o primeiro dia me integrou e me incutiu valores de rigor, trabalho de equipa, sensibilidade, respeito e responsabilidade para com o utente, motivando-me para melhorar diariamente, desenvolvendo sempre o meu espírito crítico e agindo de forma progressivamente mais autónoma, com segurança e confiança. Deixo uma palavra de agradecimento à Dra. Maria do Carmo, ao Dr. João, à Dra. Inês, à Dra. Ana, à Dra. Jéssica, ao Dr. Pedro, ao Dr. Daniel, à Dra. Márcia e à dona Júlia –

obrigado por terem contribuído de forma extraordinária na minha formação, quer profissional quer pessoal, que espero ser tão rica como a de cada um de vós.

Termino esta etapa com uma enorme sensação de gratidão e com grande motivação para encarar o que o futuro reserva, ansiosa por pôr em prática todo o conhecimento e experiência que adquiri na profissional que ambiciono tornar-me, sempre com a meta de promover a saúde e o bem-estar da comunidade em geral.

6. BIBLIOGRAFIA

FRESENIUS KABI PHARMA - **Fresubin® DB Crème.** 2021. [Consult. 10 jul. 2022]. Disponível em: https://www.fresubin.com/pt/sites/default/files/2020-08/FichaProduto_ Fresubin®DB Crème.pdf

GLINTT - **Sifarma**. 2022. [Consult. 10 jul. 2022]. Disponível em: https://www.glintt.com/pt/o-que-fazemos/ofertas/SoftwareSolutions/Paginas/Sifarma.aspx

IKEDA, Cintia Mitie *et al.* - Disfagia e melhoria do estado nutricional: Características tecno-funcionais de espessantes comerciais. **Research, Society and Development**. 10:5 (2021) e50610515244. doi: 10.33448/rsd-v10i5.15244.

INFARMED, I. P. - **Dulcolax**. 2014. [Consult. 15 jul. 2022]. Disponível em: https://extranet. infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml

INFARMED, I. P. - **Farmacêuticos**. 2021. [Consult. 22 jul. 2022]. Disponível em: https://www. infarmed.pt/web/infarmed/entidades/licenciamentos/farmaceuticos

LABORATOIRES THÉA - **HYABAK®**. 2013. Disponível em: https://thea.pt/sites/default/ files/rcm_e_fi/hyabak_ifu_04-2013.pdf

LABORATÓRIO EDOL - PRODUTOS FARMACÊUTICOS S.A - **Folheto Informativo Pandermil ® Hidrocortisona | Creme**. 2019. [Consult. 15 jul. 2022]. Disponível em: https://edol.pt/wp-content/uploads/2021/03/folheto-informativo-pandermil-creme-30g-hidrocortisona.pdf

MINISTÉRIO DA SAÚDE - Decreto-Lei n.º 95/2004, de 22 de abril. **Diário da Républica**. 2004) 2439–2441.

MINISTÉRIO DA SAÚDE - Deliberação n.º 2473/2007, de 28 de Novembro. **Diário da Républica**. 2007) 1–5.

ORDEM DOS FARMACÊUTICOS - **A Farmácia Comunitária**. 2021. [Consult. 19 jul. 2022]. Disponível em: https://www.ordemfarmaceuticos.pt/pt/areas-profissionais/farmacia-comunitaria/a-farmacia-comunitaria/

PITA, João Rui; BELL, Victoria - A farmácia em Portugal nos últimos 30 anos. Algumas reflexões sobre a farmácia de oficina ou comunitária. **Debater a Europa**. 15 (2016). doi: 10.14195/1647-6336_15_11.

SILBER, Kenneth H. *et al.* - Handbook of Improving Performance in the Workplace. Em **Handbook of Improving Performance in the Workplace**v. 2. p. 115–140.

UNIÃO EUROPEIA - Regulmento (CE) No 1223/2009 do Parlamento Europeu e do Conselho. **Jornal Oficial da União Europeia**. 2010) 151.

VALORMED - **Quem Somos** [Consult. 24 jul. 2022]. Disponível em: http://www.valormed.pt/paginas/2/quem-somos/

PARTE II

Monografia

“NSAIDS-loaded nanocarriers for next generation cancer treatment”

ABSTRACT

Nonsteroidal anti-inflammatory medications (NSAIDs) are frequently prescribed by physicians for the symptomatic treatment of pain and fever in numerous clinical situations. Numerous studies have focused their attention on the anticancer benefits of these drugs due to the anti-inflammatory properties that they possess. This is a direct result of carcinogenesis having been linked to chronic inflammation for a long time. Consequently, anti-inflammatory drugs are assumed to play a role in both the treatment and prevention of cancer. When it comes to treating cancer, NSAIDs have several drawbacks, including toxicity and adverse effects. The use of nanotechnology has made it possible to treat cancer in a way that is both safe and effective. Encapsulation of NSAIDs can be an effective way of improving drug efficacy in cancer therapy. There are several data showing the anticancer effect of NSAIDs nanomedicines. This review highlight relationship between cancer and inflammation, the role in cancer and the concept of encapsulating NSAIDs.

Keywords: Cancer; cyclogeneses-2; COX-2; nanotechnology; nanomedicines; non-steroidal anti-inflammatory drugs; NSAIDs.

RESUMO

Os medicamentos anti-inflamatórios não-esteróides (AINEs) são frequentemente prescritos por médicos para o tratamento sintomático da dor e febre em numerosas situações clínicas. Numerosos estudos centraram a sua atenção nos benefícios anticancerígenos destes medicamentos devido às propriedades anti-inflamatórias que possuem. Este é um resultado directo de a carcinogénese ter estado ligada à inflamação crónica durante muito tempo. Consequentemente, assume-se que os anti-inflamatórios desempenham um papel tanto no tratamento como na prevenção do cancro. Quando se trata de tratar o cancro, os AINS têm vários inconvenientes, incluindo a toxicidade e os efeitos adversos. A utilização da nanotecnologia tornou possível tratar o cancro de uma forma simultaneamente segura e eficaz. O encapsulamento dos AINS pode ser uma forma eficaz de melhorar a eficácia dos medicamentos na terapia do cancro. Há vários dados que mostram o efeito anticancerígeno das nanomedicinas AINEs. Esta revisão destaca a relação entre cancro e inflamação, o papel destes fármacos e o conceito de encapsular os AINEs.

Palavras-Chave: Cancro; ciclogeneses-2; COX-2; nanotecnologia; nanomedicinas; anti-inflamatórios não esteróides; AINEs.

FIGURE LIST

ABBREVIATIONS

AINEs – Anti-Inflamatórios Não-Esteróides (translation from portuguese)

AKT – Protein Kinase B

APC – Antigenic-Pesenting Cell

Bcl-2 – B-Cell Lymphoma 2

Bcl-xL – B-Cell Lymphoma Extra Large

CCLs – C-C Motif Chemokine Ligands

COX-2 – Cyclooxygenase 2

CRC – Colorectal Cancer

CSC – Cancer Stem Cell

c-SLNs – Chitosan-Coated Solid Lipid Nanoparticles

CXCL – C-X-C Motif Chemokine Ligand

DCs – Dendritic Cells

DOX – Doxorubicin

ECM – Extracellular Matrix

EGFR – Epithelial Growth Factor Receptor

EMT – Epithelial-Mesenchymal Transition

EPR – Enhanced Permeability and Retention

ERK – Signal-Regulated Kinase

FA – Ferulic Acid

GI – Gastrointestinal

GSK-3β – Glycogen Synthase Kinase-3 Beta

HA – Hyaluronic Acid

HER2 – Human Epidermal Growth Factor Receptor 2

HIF1 – Hypoxia-inducible Factor 1

HPMC – Hydroxypropyl Methylcellulose

IBD – Inflammatory Bowel Disease

IL – Interleukin

Keto-NC - Ketoprofen-Loaded Nanocapsules

NF-κB – Nuclear Factor kappa B

NLCs – Nanostructured Lipid Carriers

NPs – Nanoparticles

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

OS – Overall Survival

PEG – Polyethylene Glycol

PGs – Prostaglandins

PIA – Phospho-Ibuprofen Amid

PK – Pharmacokinetics

PLGA – Poly(lactic-co-glycolic acid)

PNPs – Polymeric Nanoparticles

PPARγ – Peroxisome Proliferator-Activated Receptor Gamma

PVA – Polyvinyl Alcohol

PVP – Polyvinylpyrrolidone

SLNs – Solid Lipid Nanoparticles

STAT3 – Signal Transducer and Activator of Transcription 3

TME – Tumour Microenvironment

TNF-α – Tumor Necrosis Factor α

TREGs – Regulatory T cells

VEGF – Vascular Endothelial Growth Factor

1. INTRODUCTION

Amidst the use of a variety of cancer treatment strategies in the clinical setting (e.g., surgery, chemotherapy, irradiation, and immunotherapy), cancer-related mortality remains one of the main causes of death worldwide, accounting for 10 million human deaths in 2020 (Sung *et al.*, 2021). Though since cancer is considered a cell-intrinsic genetic disease, most treatment approaches are aimed at directly killing tumour cells, with multidrug resistance of cancer cells being a major reason for cancer therapy's low efficacy (Tang *et al.*, 2020; Vasan, Baselga e Hyman, 2019).

Inflammation has been demonstrated heavily linked with all stages of development and malignant progression of most types of cancer, and even with the efficacy of anti-cancer therapies (Coussens e Werb, 2002; Crusz e Balkwill, 2015; Grivennikov, Greten e Karin, 2010). Rudolf Virchow proposed the association between inflammation and cancer in the mid-nineteenth century, based on observations that tumours often developed in regions of chronic inflammation and that inflammatory cells were prominent in tumour biopsies (Balkwill e Mantovani, 2001). Chronic inflammation is implicated in immunosuppression, creating a favourable microenvironment for tumorigenesis, development, and metastasis (Shacter e Weitzman, 2002). Acute inflammation increases cancer cell death by eliciting an anti-tumor immune response, whereas persistent inflammation caused by therapy promotes therapeutic resistance and cancer growth. Furthermore, anti-cancer therapies can cause inflammatory responses (Guthrie *et al.*, 2013; Schaue *et al.*, 2015). Nowadays, cancer-related inflammation is recognized as a key feature of the disease.

Non-steroid anti-inflammatory drugs (NSAIDs), due to their analgesic, antipyretic, and anti-inflammatory effects, belong to a group of widely prescribed drugs. They are commonly used as symptomatic treatment for a variety of conditions, most of them related to pain and inflammation, such as chronic inflammation, degenerative joint diseases, and acute pain. With a well-established mechanism of action, these drugs exert their effect by primarily inhibiting the enzyme cyclooxygenase (COX), crucial in the synthesis of prostaglandins (PGs) from arachidonic acid (Wong, 2019). Over the course of the last few decades, a substantial body of research has been conducted on the use of NSAIDs in the treatment and prevention of cancer. There are several papers discussing the cancer-preventive effects of NSAIDs (Ulrich, Bigler e Potter, 2006). The majority of these studies are epidemiologic in nature, in which the use of these drugs has been linked to a lower risk of developing cancer in a variety of cancer types, including breast (Dierssen-Sotos *et al.*, 2016; Harris *et al.*, 2003; Kim *et al.*, 2015),

prostate (Doat *et al.*, 2017; Vidal *et al.*, 2015), colorectal (Friis *et al.*, 2015; Ruder *et al.*, 2011), ovarian (Trabert *et al.*, 2014), and head and neck cancers (Shi *et al.*, 2017).

Conventional cancer therapies have their own inherent limitations, which led the design and application of various nanotechnologies for the purpose of making cancer treatment more effective and safer. Nanotechnologies provide powerful tools that can improve the physicochemical properties of chemotherapeutics. This can result in a reduction in the chemotherapeutics' systemic toxicity and an increase in their therapeutic index (Cho *et al.*, 2008; Martinez *et al.*, 2015). These benefits can be achieved while the chemotherapeutics' pharmacological activity and accumulation at the disease site are both increased. Encapsulating drugs inside nanocarriers and delivering them to cells in this way has several advantages: it can prevent drug degradation and metabolic deactivation, as well as increase drug solubilization, which in turn improves the drug's pharmacokinetics and biodistribution; it can facilitate selective delivery of chemotherapeutics to cancer lesions through passive or active mechanisms, which reduces off-target toxicity; and it can improve intracellular penetration (Molinaro *et al.*, 2018).

The utilization of specific NSAIDs in the treatment of cancer is restricted due to the drugs' short half-lives, low solubility, and strong affinity for protein binding. The nanosizing of such medicines can aid to improve the drugs' solubility, which may also result in increased anticancer activity. In addition, increasing the solubility and bioavailability of NSAIDs is a great way to cut down on the risk of taking excessive doses of these medications and the attendant adverse effects (Praveen *et al.*, 2022).

This review will provide an overview of the relationship between cancer and inflammation, the role of nonsteroidal anti-inflammatory drugs (NSAIDs) in cancer, and the application of nanotechnology in the treatment of cancer, in general, considering the promising next-generation cancer treatment. In addition to that, it will go into depth on the concept of encapsulating NSAIDs, either as anti-inflammatory nanomedicines or for use in cancer treatment, both of which will be discussed.

2. INFLAMMATION'S ROLE IN CANCER

As previously stated, inflammation was shown to enhance the immune response and lead to immune surveillance. Innate and adaptive immunity, which are involved in the inflammatory response, have also been shown to play a role in cancer initiation, progression, and metastasis (Figure 1).

The acute inflammatory response, which promotes innate and adaptive immune responses, is the very first line of defence against external infection or injury. The innate immune system is composed of diverse hematopoietic cells that have evolved, such as macrophages, dendritic cells (DCs) neutrophils, mast cells, and so on (Gajewski, Schreiber e Fu, 2013). These cell populations are recognized to take part in pathogen, microorganism, and necrotic substance phagocytosis, consequently mediating inflammation resolution. Furthermore, DCs and macrophages have been shown to deliver specific antigens to T cells to recognize and activate the adaptive immune response (Corrales *et al.*, 2017). As a result, acute inflammation may be able to eradicate pathogens and protect the body from infections.

Nevertheless, if the acute inflammatory response it's not limited in time, it may progress to chronic inflammation, which results in an immunosuppressive microenvironment with a great number of immunosuppressive cells (M2 macrophages, myeloid-derived suppressor cells, regulatory T cells (Tregs), etc.) and cytokines (Coussens e Werb, 2002; Mantovani *et al.*, 2008). Such changes were linked to the activation of oncogenes, DNA and protein damage, the release of reactive oxygen species, and the disruption of multiple signalling pathways such as nuclear factor kappa B (NF-κB), K-RAS, and p53, guiding to chronic diseases including cancer (Coussens e Werb, 2002). Moreover, epigenetic alterations such as DNA methylation, histone modification, chromatin remodelling, and noncoding RNA play a key role in the transformation of inflammation into cancer, including in cancer occurrence, development, invasion, metastasis, and drug resistance (Dawson e Kouzarides, 2012; Gupta *et al.*, 2018; Hanahan e Weinberg, 2011; Taniguchi e Karin, 2018).

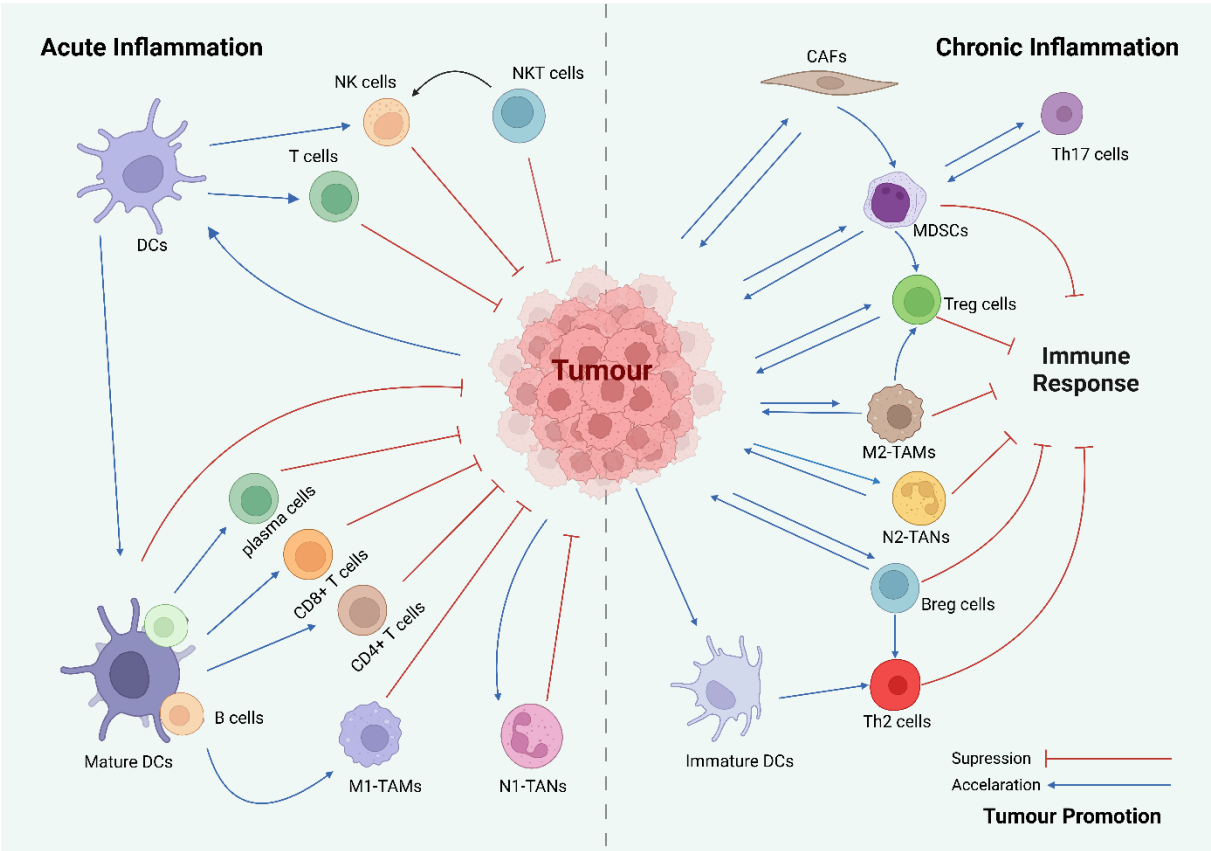

Figure 1 - The relationship between inflammation and cancer development. During acute inflammatory responses (left panel): after tumor antigen uptake or activation by TLR agonist, mature DCs can regulate anti-tumor immune responses by inducing inflammatory responses via multiple mechanisms, including cross-presenting tumor antigens and priming tumor-specific CD8+ T cells, polarizing immune cells toward tumor suppression (e.g., M1 polarization of TAMs), and recruiting NK cells that can sustain T-cell responses. Nonetheless, if the acute inflammatory response does not subside in a timely manner, it ultimately evolves into chronic inflammation (right panel). By secreting numerous cytokines, chemokines, and inflammatory mediators, cancer cells can recruit a huge number of immunosuppressive cells (e.g., MDSCs, Treg cells, Breg cells, M2-TAMs, N2-TANs, and Th2 cells) in this milieu. In turn, these immunosuppressive cells generate a thriving proangiogenic and pro-tumor microenvironment and inhibit the innate immune system and T-cell anti-tumor immune system. CAFs: cancer-associeated fibroblasts; Breg: regulatory B cell DC: dentritic cell; MDSCs: myeloid-derived supressor cells; NK: natural killer; TAMs: tumour-associated macrofags; TANs: tumour-associated neutrofils; Treg: regulatory T cell

Chronic inflammation induced by immune cells and molecular signalling pathways has been related to the human body's susceptibility to various cancers. Evidence suggests that chronic inflammatory diseases result in up to 25% of cancers; even so, the exact mechanism underlying this relation is unclear (Murata, 2018). Specific chronic inflammatory diseases were identified as precancerous tumour lesions, in particular, inflammatory bowel disease (IBD) is well known as colorectal cancer (CRC) precancerous lesion (Zhao *et al.*, 2021). Besides, the chemical induction of IBD is a well-known method for inducing CRC in mice (Jess *et al.*, 2012; Keller *et al.*, 2019)

Recurring injury and infections from some viruses and bacteria can lead to a chronic inflammatory response, for instance, infection with *H.pylori* causes ulcers, and gastritis, eventually leading to gastric cancer (Gottlieb e Nakitende, 2017; Loor e Dumitrașcu, 2016). Hepatitis B virus infection was also demonstrated cause chronic hepatitis,

and therefore progressing into primary hepatocellular carcinoma (Chen e Tian, 2019; Grivennikov e Karin, 2011).

Even cancers that develop in the absence of underlying chronic inflammation exhibit tumour-associated inflammation and inflammatory infiltrates. Oncogene activation or cell senescence caused by DNA damage can increase the transcription of pro-inflammatory genes that code for cytokines and chemokines, in which cases there is no epidemiological basis for inflammation (Mantovani *et al.*, 2008).

Both pathways converge, resulting in the activation of transcription factors in tumour cells, predominantly NF-κB, signal transducer and activator of transcription 3 (STAT3), and hypoxia-inducible factor 1 (HIF1). Such transcription factors coordinate the synthesis of inflammatory mediators like cytokines ((e.g. interferon, interleukin (IL), and tumour necrosis factor (TNF)-α)) and chemokines (C-X-C Motif Chemokine Ligand (CXCL), C-C motif chemokine ligands (CCLs)), and the production of cyclooxygenase 2 (COX-2) (which results in the biosynthesis of prostaglandins (PGs)). These factors recruit and enable a variety of leukocytes, most notably myelomonocytic cells. Smouldering cancer-related inflammation promotes tumour growth in a variety of ways (Mantovani *et al.*, 2008).

NF-κB or STAT3 activation is found in more than half of all cancers and is required for the expression of a variety of target genes important for tumorigenesis, including anti-apoptotic genes (inhibitor of apoptosis, B-cell lymphoma (Bcl-xL and Bcl-2), cellular FLICE-like inhibitory protein, proliferative genes (Cyclins, c-Myc), stress-response genes, ferritin heavy chain, chemokines, and pro-angiogenic molecules, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, CXCL4, CXCL8, and CLX12 (Grivennikov e Karin, 2010; Karin, 2008; Kujawski *et al.*, 2008; Niu *et al.*, 2008). In comparison, in immune cells, NF-κB and STAT3 are required to produce pro-inflammatory cytokines such as IL-1, IL-6, IL-12/IL-23, and TNF, which mediate NF-κB and STAT3 activation in cancer cells.

The process of epithelial-mesenchymal transition (EMT), which is required for metastasis, can be stimulated by cytokines like TGF, IL-1, TNF-, and IL-6 (Voronov *et al.*, 2003; Wu *et al.*, 2009; Yang e Weinberg, 2008) and may be an outcome of NF-κB and STAT3 activation (Yu, Kortylewski e Pardoll, 2007) via induction of EMT regulators such as Snail, ZEB, and Twist (Sullivan *et al.*, 2009; Wu *et al.*, 2009). Chemokines and cytokines are important for the formation and spread of tumours via the same mechanisms that affect primary tumour growth and survival. Chemokines can direct malignant cell migration towards blood vessels,

whereas cytokines like TNF can increase vascular permeability (Condeelis e Pollard, 2006; Luo *et al.*, 2004; Nguyen, Bos e Massagué, 2009).

Lastly, therapy-induced inflammation is a type of inflammatory response associated with cancer. Because most cancer cells are resistant to apoptosis, chemo- or radiotherapy-induced death is necrotic, and necrotic proteins are potent inducers of inflammation (Tesniere *et al.*, 2008). Inflammatory mediators produced by dying cancer cells can activate tumour-infiltrating macrophages that produce cytokines, activating the oncogenic transcription factors in remaining cancer cells, promoting their survival and proliferation (Yu, Kortylewski e Pardoll, 2007). The delicate balance between therapy-induced tumour eradication and regrowth depends on the extent of therapy-induced cell death, the type of cancer being treated, and the tumour microenvironment (TME).

2.1. COX-2, Prostaglandin Synthesis, and Cancer

The production of COX-2, and sequentially the synthesis, by the activation of the signaling pathways of NF-κB, STAT3, and HIF1, influence positively tumour development. COX-2 has been reported to be frequently overexpressed in several cancers including prostate (Fujita *et al.*, 2002), breast, lung, colon (Soslow *et al.*, 2000), and pancreatic cancer (Molina *et al.*, 1999; Okami *et al.*, 1999). The upregulation of these enzymes plays a key role in cancer progression by stimulating tumour cell proliferation, angiogenesis, inflammation, invasion, metastasis, and apoptosis resistance (Hashemi Goradel *et al.*, 2019; Xu *et al.*, 2014).

In both cancer cells (Charalambous *et al.*, 2003) and tumour-associated macrophages (Hung *et al.*, 2004), NF-κβ contributes to COX-2 activation, with p65, an NF-κβ protein-related, being identified for its role in the induction of this enzyme in cancer cells (Cai *et al.*, 2017; Hao *et al.*, 2017). COX2/STAT3 signalling promotes an immunosuppressive microenvironment (Maturu *et al.*, 2017), EMT (Tong *et al.*, 2017), and cancer cell proliferation (Ramu *et al.*, 2018). This signalling could be a component of the NF/COX2/BCL2/IL6/STAT3 pathway (Das *et al.*, 2017). HIF-1α is a target for COX-2 and a marker of angiogenesis in cancer cells (Maturu *et al.*, 2017; Mortezaee, 2018). The existing interaction between COX-2 and HIF1 contributes to the induction of hypoxia within the TME. HIF-1α acts as a positive inducer of COX-2 expression and COX-2/HIF-2α is linked to cancer cell resistance to chemotherapeutic drugs in hypoxic conditions (Dong *et al.*, 2018; Greenhough *et al.*, 2009).

It is broadly acknowledged that COX-2 contributes to carcinogenesis via PG overproduction. PGE2 exerts its effects via interaction with its putative transmembrane G-

protein-coupled EP receptors (EP1-EP4), particularly EP1 and EP4 (Majumder *et al.*, 2015, 2018; Pan *et al.*, 2016). COX-2 action on PGs, particularly PGE2, is responsible for many processes in favor of tumour promotion, such as angiogenesis through upregulation of VEGF and tumour growth by overexpression of epithelial growth factor receptor (EGFR) (Hosseini *et al.*, 2018; Todoric, Antonucci e Karin, 2016) or maintenance of cancer stem cell (CSC)-like activity via activation of WNT/β-catenin/TCF (Greenhough *et al.*, 2009) and miR526b (Majumder *et al.*, 2015), and suppression of dual specificity phosphatase 2 (Hou *et al.*, 2017). This positive feedback loop between COX-2 and PGE2 is also accountable for metastasis by upregulation of matrix metalloproteinases type 2 and 9 (Hosseini *et al.*, 2018; Todoric, Antonucci e Karin, 2016) and IL-11 (Singh *et al.*, 2006) along with activation of oncogenic miR526b (Majumder *et al.*, 2015), as well as cancer cell invasion via extracellular signal-regulated kinase (ERK) (Majumder *et al.*, 2018) and membrane proteases upregulation (Ko *et al.*, 2017) and cell survival (Majumder *et al.*, 2018) and inflammation (Ramu *et al.*, 2018) through interaction with PI3K/AKT. Modulation of the immune system through an increase in the activity of Tregs (Sharma *et al.*, 2005) via induction of Nr4a expression (Hibino *et al.*, 2018) and the activity of protumour M2 cells (Esbona *et al.*, 2018) is another consequence of the PGE2 response. COX-2 can instruct an immune phenotype by recruiting immune cells into tumour tissue, resulting in an immunosuppressive state in the tumour milieu (Lang *et al.*, 2006) in favour of cancer cell activation (Höing *et al.*, 2018). COX2/PGE2 released by cancer cells into this milieu inhibits host immunological responses to tumour-derived antigens by blocking cytotoxic T lymphocyte activity (Miao *et al.*, 2017).

3. NSAIDs AS ANTICANCER ENTITIES

NSAIDs, for example, indomethacin, sulindac, aspirin (acetylsalicylic acid), ibuprofen, and piroxicam among others, are structurally diverse groups of similarly acting compounds. They have a variety of pharmacological effects. However, at physiologically relevant concentrations, their anti-inflammatory action is primarily due to their ability to inhibit the cyclooxygenase activity of the COX enzymes, which reduces prostaglandin production (Vane e Botting, 1998).

There's been a substantial body of scientific research on the use of NSAIDs in cancer treatment and prevention over the last few decades, whereas the link between chronic inflammation and cancer has long been discovered (Balkwill e Mantovani, 2001). One plausible answer for researchers' interest in NSAIDs for cancer prevention is their well-known anti-inflammatory properties, as many malignancies are linked to inflammation, as demonstrated by

the evidence (Rakoff-Nahoum, 2006). As a result, it stands to reason that drugs that inhibit inflammation could be useful in cancer prevention or treatment. As COX inhibitors, NSAIDs are inevitably an attractive candidate for cancer therapy and chemoprevention. Since certain of the by-products of COX activity (such as PGE2) are involved in carcinogenesis, blocking COX may be seen as an effective therapy. PGE2 is increased in cancer cells (Roberts *et al.*, 2011) and stimulates cancer cell invasion and proliferation (Ke *et al.*, 2016). Apart from their anti-inflammatory properties, NSAIDs' ability to induce apoptosis, inhibit angiogenesis, and enhance cellular immune responses may all contribute to their anticancer effects (Figure 2) (Thun, Jane Henley e Patrono, 2002).

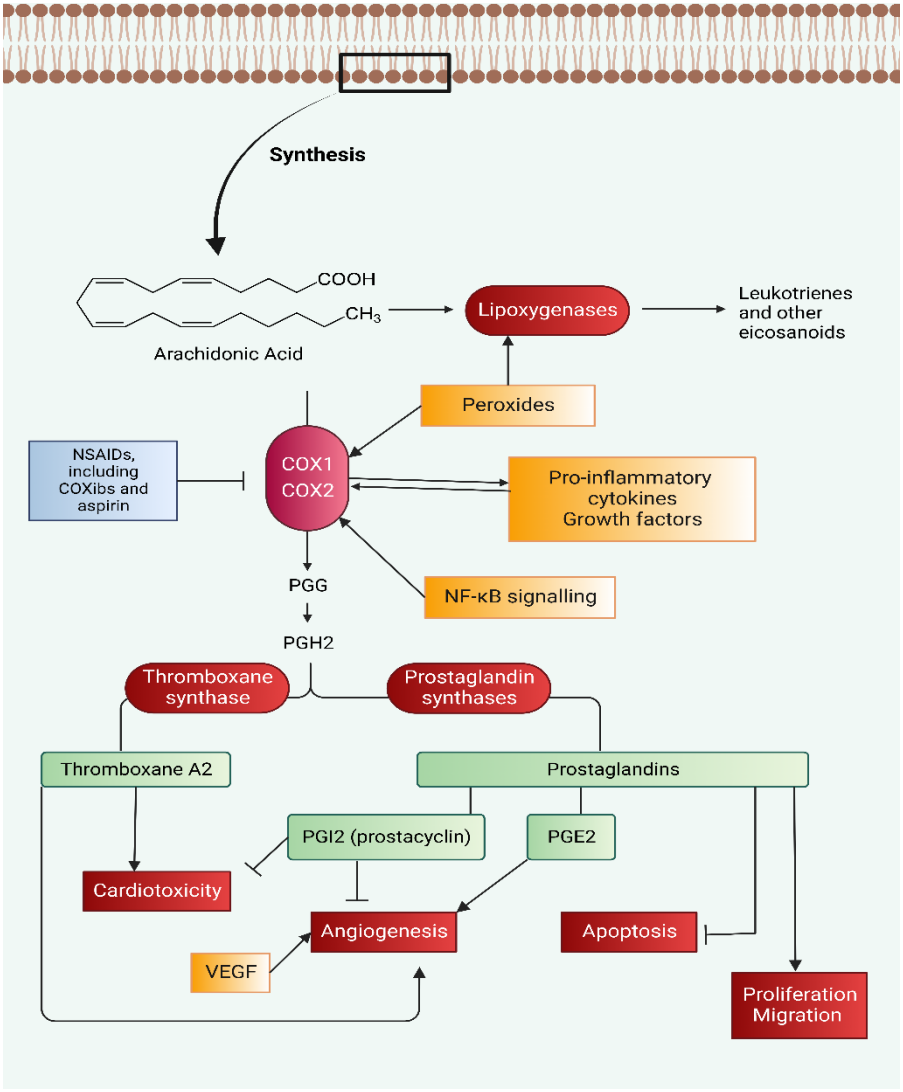

Figure 2 - NSAIDs, COX inhibition and prostaglandins. COX1 and COX2 – enzymes important to the conversion of arachidonic acid to prostaglandins — are the primary targets of cyclooxygenase 2 (COX2)-specific inhibitors (COXibs) and non-steroidal anti-inflammatory medicines (NSAIDs). In an alternate pathway for arachidonic acid metabolism, lipoxygenases are involved. Peroxide concentrations influence both the lipoxygenase and COX pathways, with COX2 being triggered at lower peroxide concentrations than COX1. Angiogenesis, apoptosis, cell proliferation, and migration are all influenced by prostaglandins (PGs). The equilibrium between prothrombotic factors (such as thromboxane A2) and anti-thrombotic factors (such as prostacyclin) may have a significant bearing on cardiovascular damage. NF-κB, nuclear factor-κB; VEGF, vascular endothelial growth factor.

The published literature is replete with data on the cancer-protective effects of NSAIDs. Several studies have demonstrated that these drugs are related with a lower cancer risk in several cancer types, including prostate (Downer *et al.*, 2019; Hurwitz *et al.*, 2019; Jacobs *et al.*, 2011; Vidal *et al.*, 2015), breast (Brasky *et al.*, 2014; Clarke *et al.*, 2017; Coghill *et al.*, 2012; Kehm *et al.*, 2019; Kirsh *et al.*, 2007), ovarian (Barnard *et al.*, 2018; Merritt *et al.*, 2018; Peres *et al.*, 2016; Trabert *et al.*, 2014), and colorectal (Amitay *et al.*, 2019; Chen *et al.*, 2021; Hung *et al.*, 2004; Rodríguez-Miguel *et al.*, 2019; Ruder *et al.*, 2011). Moreover, evidence show that in pancreatic and lung cancer, the use of NSAID's might also reduce cancer risk (Bradley *et al.*, 2010; Dong *et al.*, 2018; Khuder *et al.*, 2005; Poku *et al.*, 2020; Zhang *et al.*, 2015).

3.1. Evidence from In Vitro and In Vivo Studies

Experimental studies have been conducted to investigate the underlying mechanisms of NSAID's anticancer effects using cell lines or animal models. Aspirin has been shown to exert anticancer effects. Xiang *et al.* determined that aspirin has antiapoptotic and antiproliferative effects on HeLa cells. In these cervical cancer cells, there was a time-and dose-dependent reduction in ErbB2 expression, whereas the underlying mechanism of aspirin's antiapoptotic effects was due to its inhibition of the activation of ERK and protein kinase B (AKT), as well as the inhibition of Bcl-2 expression (Xiang *et al.*, 2010).

Similarly, multiple nonaspirin NSAIDs, including celecoxib (Alshafie *et al.*, 2000) and loxoprofen (Yao *et al.*, 2005), were shown to protect against cancer. In an in vivo study employing a rat mammary model, Celecoxib revealed 90% tumour regression and a 25% reduction in the number of palpable tumours (Alshafie *et al.*, 2000). Ibuprofen inhibited cell proliferation in mouse and human colorectal cells, according to another study. The same study found a 40%-80% inhibition of tumour growth and a reduction in liver metastases in mice with colorectal cancer (Yao *et al.*, 2005). Mice treated with the drug had significantly lower intratumoral vessel density and mRNA expressions of VEGF in the tumour, while non-small cell lung cancer patients treated with loxoprofen (120 mg/day) for one week had substantially lower plasma levels of VEGF. The study's study results point to the possibility of suppressing angiogenesis by inhibiting VEGF (Kanda *et al.*, 2003).

Surprisingly, many of the NSAIDs anticancer effects are not dependent on COX inhibition. NSAIDs have antiproliferative and apoptotic effects on cell lines regardless of their level of COX expression (Aggarwal *et al.*, 2000; Vogt *et al.*, 2001). The fact that prostaglandin supplementation does not reverse the growth-suppressing effects of NSAIDs in cancer shows

that NSAIDs suppress cancer via COX-independent mechanisms (Chan *et al.*, 1998). In one study, indomethacin was shown to induce apoptosis in esophageal adenocarcinoma cells through COX-2-independent Bax upregulation and mitochondrial cytochrome C translocation (Aggarwal *et al.*, 2000). Another study (Vogt *et al.*, 2001) discovered that COX-2-independent NSAIDs induce apoptosis in malignant melanomas.

Suppression of AKT signalling, inhibition of NF-κB signalling, induction of peroxisome proliferator-activated receptor gamma (PPARγ) promoter activity, inhibition of AMP-activated protein kinase, inhibition of metastasis and angiogenesis, and modulation of cGMP phosphodiesterase signalling are other NSAID COX-independent cancer therapies (Gurpinar, Grizzle e Piazza, 2014). Celecoxib, Etoricoxib and Diclofenac were found to inhibit inflammatory pathways in colon cancer. The co-administration of these drugs leads the downregulation of NF-kB expression, the upregulation of the PPARγ, along with the increase the number of apoptotic cells (Ghanghas *et al.*, 2016). Besides that, NSAID treatment induced hallmarks of immunogenic cell death (ICD) in CRC cells and colonic epithelial cells upon loss of antigenic-presenting cell (APC) tumour suppressor, and elevated tumour-infiltrating lymphocytes in the polyps of APCMin/+ mice. At the same time, NSAIDs instigate endoplasmic reticulum stress and BID-mediated immunogenic cell death to restore immunosurveillance and suppress colorectal tumour formation (Fletcher *et al.*, 2021).

3.2. Evidence from Epidemiologic Studies

Numerous epidemiologic studies have been conducted to investigate the cancer-protective effects of both aspirin and nonaspirin NSAIDs. Many of these studies have focused on cancers of the gastrointestinal (GI) tract. Observational studies have demonstrated that taking aspirin and other NSAIDs reduces the incidence of both colorectal adenomas and carcinomas. Although the variation within and between studies, the amount of the effect is remarkably stable, despite differences in NSAIDs, dosage regimes, length of use, and research groups (Din *et al.*, 2010). A study that involved 5129 colorectal cancer (CRC) cases and 4093 controls investigated the association between the use of NSAIDs and aspirin and CRC risk. Substantial evidence showed that ever regular use of NSAIDs (including aspirin) and aspirin alone was associated with a 34% (95% CI 26%, 41%) and 27% (95% CI 17%, 35%) lower risk of CRC respectively. Additionally, there was no significant associations between the use of this drugs and genetic risk (NSAIDs= OR for interaction 0.99, 95% CI 0.97, 1.00, P = 0.10; aspirin= OR for interaction 0.99, 95% CI 0.97, 1.01, P = 0.22) (Chen *et al.*, 2021). In another study, findings reveal that nonaspirin-NSAIDs have a statistically significant chemoprotective

impact against CRC ranging from 30% to 60%, depending on the duration of treatment (Rodríguez-Miguel *et al.*, 2019).

However, due the long-term use of aspirin in cardiovascular diseases, it's the NSAID's with more evidence for their chemoprevention proprieties. A study conducted by Bastiaannet *et al.* shown that aspirin lead to a significant reduction of mortality users (independent of the frequency) as compared with non-users with a RR of 0.62 (95%CI 0.46–0.80; p=0.001). Additionally, the use of aspirin after a diagnosis of colorectal cancer has been linked to a significant reduction in overall mortality and a higher chance of survival among patients with the disease (Bastiaannet *et al.*, 2012). Rothwell *et al.* studied the long-term effect of aspirin on the incidence and mortality of colorectal cancer in four randomized trials (the Thrombosis Prevention Trial, the British Doctors Aspirin Trial, the Swedish Aspirin Low-Dose Trial, and the UK-TIA Aspirin Trial) for 20 years. The planned treatment time was 6 years, and the median follow-up period was 18.3 years. 391 (2.8%) of the 14033 patients had colorectal cancer. There was a considerable reduction in the risk of colon cancer within next 20 years (incidence hazard ratio (HR) 0.76, 0.60-0.96, p=0.02; mortality HR 0.65, 0.48-0.88, p=0.005) but still not rectal cancer (0.90, 0.63-1.30, p=0.58; 0.80, 0.50-1.28, p=0.35). Regrettably, there's no actual advantage for aspirin doses greater than 75 mg daily or a duration of more than 5 years of routine treatment with 75-300 mg of aspirin daily. (Rothwell *et al.*, 2010). This is reinforced by data from two large studies, the Nurses' Health Study (NHS,1980-2010) and the Health Professionals Follow-Up Study (HPFS,1986-2012), which found a reduction in overall cancer risk (RR=0.97; % CI:0.94,0.99), owing primarily to a reduced incidence of GI cancers, particularly colorectal cancers (Cao *et al.*, 2016).

Although for CRC the outcomes are well established, they are less apparent in other cancers. In the Sister Study, which looked at women who had a sister who had breast cancer, there were 2118 incident breast cancers among the 50,884 women who participated. The use of nonaspirin, noncoxib NSAIDs wasn't linked to a lower risk of breast cancer in postmenopausal women. Regrettably, for premenopausal women, any nonaspirin NSAID (HR_{4vs1} = 0.66, 95 percent CI: 0.50-0.87) and aspirin specifically (HR_{4vs1} = 0.57, 95 percent CI: 0.33-0.98) reduced the risk of breast cancer. The study revealed that those with a high risk of breast cancer, including having a sister with the disease, may gain from using NSAIDs as a chemoprevention method (Kim *et al.*, 2015). Further research found a moderate 20% decrease in risk of developing HR-positive/HER2-negative breast cancer was noticed in the 23% of women who reported using low-dose aspirin at least three times a week, which is mainly accountable for the similar association reported among NSAID use and risk of breast cancer

overall (Clarke *et al.*, 2017). In its turn, there are other finds that contradict or find inconclusive the chemoprevention action of NSAID's in breast cancer (Bens *et al.*, 2019; Cairat *et al.*, 2021; Cronin-Fenton *et al.*, 2010; Li *et al.*, 2012). The relationship between NSAID's and breast cancer is dependent on the molecular subtype of the cancer. A population-based case control study in Western New York found that ibuprofen use was associated with an increased risk of ER+/PR+ (OR 1.33, 95 percent CI: 1.09-1.62), HER2- (OR 1.27, 95% CI: 1.05-1.53), and p53- breast cancers (OR 1.28, 95% CI: 1.04-1.57) breast cancers (Brasky *et al.*, 2011). These findings are consistent with an earlier study (Nurse's Health Study II), which found that using nonaspirin NSAIDs 2-3 times per week was associated with an increased risk of breast cancer (RR 1.37, 95 percent CI: 1.09-1.67), but hormone receptor status did not play a role in this study (Eliassen *et al.*, 2009). The underlying mechanisms of this association and increased risk of breast cancer are unclear, and more research is needed.

NSAIDs were associated with a decreased risk of cancers originating from the reproductive system in both sexes, apart from cancers of the gastrointestinal tract and breast cancer. In a study involving 819 prostate cancer patients and 880 controls, NSAIDs were found to be associated with a decrease in the chance of prostate cancer in men. All NSAIDs were inversely related to a lower risk of prostate cancer (OR 0.77, 95% CI: 0.61–0.98), particularly drugs that selectively inhibit COX-2 (OR 0.48, % CI: 0.28–0.79). Men with severe prostate cancer who used nonaspirin NSAIDs had a reduced risk (OR 0.49, 95% CI: 0.27–0.89), as did nonaspirin users with a history of prostatitis (OR 0.21, 95% CI: 0.07–0.59).This association was not statistically significant ($p > 0.05$) (Doat *et al.*, 2017) In the same study, using pooled data from 12 population-based studies involving 7776 cases and 11843 controls, found that women with ovarian cancer had a decreased cancer risk. Aspirin, but not NSAIDs, has been linked to a decreased risk of ovarian cancer (OR 0.91; 95% CI: 0.84 to 0.99) (Trabert *et al.*, 2014). Another research suggests that women who use aspirin daily have a 10 percent lower risk of developing ovarian cancer, which was more effective for low-dose and daily users, compared to women who use aspirin infrequently or not at all. This risk reduction was comparable to that observed in case–control studies (Trabert *et al.*, 2019).

Although NSAID's had demonstrated to have a high potential for chemoprevention and even anticancer therapy, its sides effects must not be overlooked. It is broadly acknowledged that NSAIDs are linked to a higher risk of acute myocardial infarction, GI side effects ranging from mild discomfort, nausea, and dyspeptic symptoms to severe complications such as bleeding, peptic ulcer perforation, and intestinal obstruction, as well as renal side effects, which in severe cases may lead to renal failure (Wong, 2019). Thus, to introduce

NSAIDs as active and prolonged therapy, it is necessary to overcome the side effects they produce, and the delivery of these drugs through nanoparticles may be a viable option.

4. NANOPARTICLES FOR CANCER THERAPY

Nanotechnology's uniquely appealing characteristics for imaging, diagnosis, and drug delivery, synthetic vaccine development and miniature medical devices, as well as the therapeutic nature of some nanomaterials themselves, are largely responsible for the growing interest in its application to cancer (Kearney e Mooney, 2013; Peer *et al.*, 2007; Shi *et al.*, 2010; Swartz, Hirosue e Hubbell, 2012). Nanotherapies that contain some of these characteristics (such as enhanced circulation and reduced toxicity) are already in use, while others are showing great promise in clinical testing, with definite findings anticipated soon (Wolfram e Ferrari, 2019). Numerous therapeutic nanoparticle (NP) platforms, including liposomes, albumin NPs, and polymeric micelles, were approved for the treatment of cancer, and numerous other nanotechnology-enabled therapeutic modalities, like chemotherapy, gene or RNA interference (RNAi) therapy, radiation therapy, hyperthermia, and immunotherapy, are undergoing clinical investigation (Shi *et al.*, 2017) (Table 1).

Table 1 - Examples of clinical-stage nanomedicines for cancer therapy.

Generic name and/or Proprietary name	Nano platform	Active Pharmaceutical Ingredients	Cancer Type	Status	Ref.
Chemotherapy: non-targeted delivery					
Liposomal Doxorubicin (Doxil)	Pegylated Liposome	Doxorubicin	HIV-related Kaposi sarcoma, ovarian cancer and multiple myeloma	Approved by FDA	(Smith, 2013)
Liposomal Daunorubicin (DaunoXome)	Liposome	Daunorubicin	HIV-related Kaposi sarcoma	Approved by FDA	(Smith, 2013)
Liposomal Irinotecan (Onivyde or MM-398)	Pegylated liposome	Irinotecan	Post-gemcitabine metastatic pancreatic cancer	Approved by FDA	(Inman, 2015)
Liposomal Doxorubicin (Myocet)	Liposome	Doxorubicin	Metastatic Breast cancer	Approved in Europe and Canada	(Smith, 2013)
Mifamurtide (Mepact)	Liposome	Muramyl tripeptide phosphatidylethanolamine	Nonmestastatic, resectable osteosarcoma	Approved in Europe	(Smith, 2013)
Nab-paclitaxel (Abraxane)	Albumin NP	Paclitaxel	Breast, lung and pancreatic cancer	Approved by FDA	(Smith, 2013)
Polymeric micelle paclitaxel (Genexol-PM)	Polymeric micelle	Paclitaxel	Breast cancer and NSCLC	Approved in Korea	(Smith, 2013)
Liposomal cisplatin (Lipoplatin)	Pegylated liposome	Cisplatin	NSCLC	Phase III	(Stathopoulos *et al.*, 2010)

NK-105	Polymeric micelle	Paclitaxel	Metastatic or recurrent breast cancer	Phase III	(US National Library of Medicine, 2016)
Chemotherapy: targeted delivery					
MM-302	HER2-targeting liposome	Doxorubicin	HER2-positive breast cancer	Phase II/III	(US National Library of Medicine, 2016)
MBP-426	TfR-targeting liposome	Oxaliplatin	Gastric, oesophageal and gastro-oesophageal adenocarcinoma	Phase I/II	(US National Library of Medicine, 2014)
Anti-EGFR immunoliposomes loaded with doxorubicin	EGFR-targeting liposome	Doxorubicin	Solid tumours	Phase I	(US National Library of Medicine, 2014)
Chemotherapy: stimuli-responsive delivery					
ThermoDox	Liposome	Doxorubicin	Hepatocellular carcinoma	Phase III	(US National Library of Medicine, 2016)
Chemotherapy: combinatorial delivery					
Liposomal cytarabine-daunorubicin (CPX-351 or Vyxeos)	Liposome	Cytarabine and daunorubicin (5:1)	High-risk acute myeloid leukaemia	Phase III	(US National Library of Medicine, 2016)
CPX-1	Liposome	Irinotecan and floxuridine (1:1)	Advanced colorectal cancer	Phase II	(US National Library of Medicine, 2016)
Hyperthermia					
NanoTherm	Iron oxide NP	NA	Glioblastoma	Approved in Europe	(Smith, 2013)
AuroLase	Silica core with a gold nanoshell	NA	Head and neck cancer, and primary and metastatic lung tumours	Pilot study	(US National Library of Medicine, 2016)
Radiotherapy					
NBTXR3	Hafnium oxide NP	NA	Adult soft tissue sarcoma	Phase II/III	(US National Library of Medicine, 2016)
Gene or RNAi therapy					

SGT53	TfR-targeting liposome	Plasmid encoding normal human wild-type p53 DNA	Recurrent glioblastoma and metastatic pancreatic cancer	Phase II	(US National Library of Medicine, 2016, 2016)
SNS01-T	Polyethylenimine NP	siRNA against eIF5A and plasmid expressing eIF5A-K50R	Relapsed or refractory B cell malignancies	Phase I/II	(US National Library of Medicine, 2014)
Atu027	Liposome	siRNA against protein kinase N3	Advanced or metastatic pancreatic cancer	Phase I/II	(US National Library of Medicine, 2016)

FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung cancer;

Medical nanotechnology utilizes nanoscale materials, which are typically 1–100 nm in size. These materials are used in the design and manufacture of therapeutic devices and drugs (Ali *et al.*, 2021). Nanomaterials are distinguished from conventional macromolecules by their distinctive magnetic, electrical, and optical properties, which emerge as their size approaches the nanoscale. Typical nanomaterials share the following traits: a high surface-to-volume ratio, improved electrical conductivity, spectral shift of optical absorption, superparamagnetic behaviour, and distinctive fluorescence properties. In the medical field, nanoparticles can be employed for regulated drug delivery. They also improve permeability allowing passage across biological barriers and enhanced biocompatibility (Cheng *et al.*, 2021). Such characteristics of nanomaterial indicate that it could be exploited in cancer treatments. The high surface-to-volume ratio of some nanomaterials can combine with biomolecules or residues, that can increase the specificity of chemical drug complex in targeted therapy, hence improving the efficacy of nanomaterial-based treatment while decreasing its toxicity (Song *et al.*, 2010).

Several conventional cancer treatment methods have been widely implemented so far. Additionally, despite variances in working platforms, functional ingredients, and methods, many of the researchers focus on two primary targets: tumour cells and the TME, which includes the immune system associated with the tumour.

Targeted delivery is one of the primary benefits of nanomaterial-based cancer therapy versus conventional medications. Recent advancements have been made in nanomaterial-based targeted delivery. The concept of targeted delivery entails the specific targeting of specific cancer cells, which can be accomplished through passive or active targeting. Passive targeting utilizes the enhanced permeability and retention (EPR) effect, whereas active targeting is

performed by conjugating with antibodies, peptides, aptamers, and small compounds. Targeted delivery reduces toxicity in normal cells, protects pharmaceuticals from degradation, and increases half-life, loading capacity, and solubility compared to free medications (Ali *et al.*, 2021; Rosenblum *et al.*, 2018). Using EPR and active targeting, altered nanocarriers such NPs, dendrimers, and carbon nanomaterials can reach cancer cells and release chemical drugs or biomaterials (Maghsoudnia *et al.*, 2020; Zhang *et al.*, 2014). Antibodies that target specific antigens which are upregulated on the surfaces of cancer cells are commonly utilized in these platforms. Depending on the enclosed cargo, cancer cells endocytose encapsulated chemical medicines that exert cytotoxicity or nucleic acid contents that promote cell apoptosis. Nucleic acid delivery has advanced, and nano-drug delivery systems based on exosomes (Jeong *et al.*, 2020; Zhang *et al.*, 2020), polymeric nanoparticles (PNP), liposomes (Roy, Ghose e Biswas, 2022), and dendrimers (Tarach e Janaszewska, 2021) are being intensively studied in cancer therapy.

Another approach focuses on the TME containing tumour cells. Sengupta created an NP system targeting aberrant tumour angiogenesis with combretastatin, which was co-encapsulated with doxorubicin (DOX) in the poly(lactic-co-glycolic acid) (PLGA) core. Consequently, the DOX was readily taken up by the tumour following combretastatin-induced fast closure of the malignant vessels, and an increased overall therapeutic index together with lower toxicity was attained (Sengupta *et al.*, 2005). Extracellular matrix (ECM) has also been studied in cancer treatment, in addition to aberrant vasculature. Cancer proliferation, migration, invasion, and angiogenesis are guided by ECM (Trédan *et al.*, 2007). In the design of nanocarriers, ECM is one of the elements to be considered. Recombinant human hyaluronidase (PEGPH20) in PEGylated form that targets ECM hyaluronic acid demonstrated therapeutic effects for metastatic pancreatic cancer patients, particularly those with high hyaluronidase expression (Hingorani *et al.*, 2016). Coating nanocarriers with hyaluronidase has been attempted to improve the ability of chemically loaded nanocarriers to penetrate solid tumours. This straightforward but effective technique demonstrates enhanced antitumor effectiveness (Chen *et al.*, 2020).

Nano-drugs can preserve superior selectivity, bioavailability, reduced cytotoxicity to normal tissue, a larger loading capacity, a longer half-life period, and distinctive drug release patterns, thereby overcoming the drawbacks of conventional chemical therapy. During the past two decades, significant advances in cancer pathology and nanoscience, technology, and industry have produced an abundance of nanomaterials for cancer diagnosis and treatment (Cheng *et al.*, 2021).

However, only a small proportion of nano-drugs have been successfully produced and implemented into clinical practice (Figure 4).

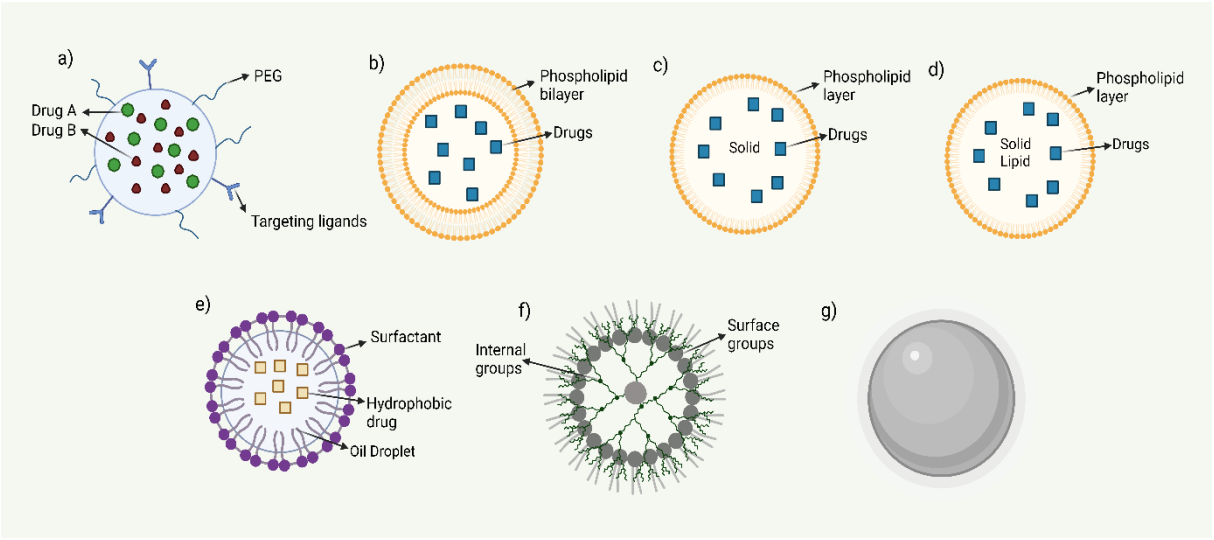

Figure 3 - Categories of nanomaterials applied in cancer treatment. a) Nanoparticles. b) Liposomes. c) Solid lipid nanoparticles. d) Nanostructured lipid carriers. e) Nanoemulsions. f) Dendrimers. Metallic nanoparticles. PEG, poly(ethylene glycol)

Polymeric nanoparticles (PNPs), metallic nanoparticles, extracellular vesicles, monoclonal antibodies (mAb) nanoparticles are broadly explored nanoparticles (NPs). PNPs serve as drug carriers, transporting chemical drugs to malignant locations and allowing for the controlled release of the pharmaceuticals over time (Masood, 2016). Because of their unique characteristics and architectures, these enhanced polymeric nanoparticles offer several significant benefits. PNPs are useful tools for increasing the stability of volatile pharmaceutical agents. When it comes to chemical drugs, PNPs offer a wider range of administration options, including oral and intravenous dosing, in addition to a higher loading capacity than free drugs. This ability that protects drugs from degradation helps minimize unwanted toxicity to normal tissues; for instance, the ability that protects drugs from degradation helps minimize undesired toxicity to normal tissues (Cheng *et al.*, 2021).

Albumin is used as a therapeutic carrier for the delivery of hydrophobic chemotherapeutics using the nanoparticle albumin-bound (nab) platform developed by nanotechnology. Through a process of reversible noncovalent binding, albumin serves as a natural transporter of hydrophobic compounds. Additionally, albumin can attach to the glycoprotein (gp60) receptor, which enables it to facilitate the transcytosis of molecules that are linked to albumin. The combination of these desirable qualities resulted in the development of the nab technology, which is a nanoparticle that is made up of albumin and bound hydrophobic medicines (Wang, Langer e Farokhzad, 2012). The commercialization of NP albumin-bound paclitaxel was the second class of nanomedicines. Upon intravenous

administration, nab-paclitaxel rapidly dissociates into its albumin and paclitaxel constituents and has not been shown to significantly change the pharmacokinetics (PK) and biodistribution of paclitaxel. Although the every-3-week dosing schedule of nab-paclitaxel is superior to paclitaxel in terms of response rate and time to progression in patients with breast cancer (Gradishar *et al.*, 2005), a once-per-week dosing schedule did not demonstrate similar trends in progression-free survival or overall survival and demonstrated increased toxicity (Rugo *et al.*, 2015).

Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are the three main categories that have been receiving a great deal of attention in current research and clinical trials. Liposomes are vesicles that take the shape of spheres and are composed of an aqueous core and a vesicle shell. They are made up of a single or many bilayered membrane structures that might be constructed of natural or synthesized lipids (Svenson, 2012). They can be as small as tens of nanometers or as large as micrometres in size, depending on the design chosen for them. Liposomes are effective therapeutic carriers due to their biocompatible and biodegradable composition, as well as their unique ability to encapsulate hydrophilic drugs in their aqueous core and hydrophobic molecules within their lamellae. Liposomes may also be coated with polymers such as polyethylene glycol (PEG) in order to increase both their stability and the amount of time they spend in circulation. In most cases, the PK and biodistribution of a drug are enhanced when it is formulated using a liposomal delivery system (Molinaro *et al.*, 2018). Liposomes were the first class of therapeutic NPs to receive clinical approval for the treatment of cancer (Barenholz, 2012), for example, liposomal DOX; Doxil and Myocet. Along with other lipid-based NPs, still represent a large proportion of nanotherapeutics that are in the clinical stage. While it has been demonstrated that encapsulating drugs in liposomes can improve PK and biodistribution, there are currently no commercially available liposomal therapeutic agents that have shown an improvement in overall survival (OS) if directly compared with the conventional parent drug (Petersen *et al.*, 2016). In patients with high-risk acute myeloid leukemia, the most recent phase III results of liposomal cytarabine–daunorubicin (Vyxeos; also known as CPX-351) showed improved OS of 9.56 months versus 5.95 months when compared with the standard of care regimen of cytarabine and daunorubicin (Celator Pharmaceuticals, 2016).

NPs have also shown potential for the delivery of numerous new anticancer therapeutic agents, in addition to their commonly reported use as carriers for chemotherapeutics. These new anticancer therapeutic agents include molecularly targeted agents (Ashton *et al.*, 2016), antisense oligonucleotides (Dritschilo *et al.*, 2006; Elazar *et al.*,

2010), small interfering RNA (siRNA) (Davis *et al.*, 2010; Jensen *et al.*, 2013; Schultheis *et al.*, 2014; Tabernero *et al.*, 2013), and mRNA (Islam *et al.*, 2015), as well as DNA inhibitor oligonucleotides (Tolcher *et al.*, 2014). In addition, genetic and chemical engineering approaches have made it easier to deploy viral nanoparticles (NPs) as vehicles for the delivery of therapeutic agents (Yildiz, Shukla e Steinmetz, 2011). Examples of this include the use of adeno-associated virus for the treatment of lipoprotein lipase deficiency, which has been approved by the European Commission (Ylä-Herttuala, 2012); lentivirus, which is currently being tested in a number of clinical trials for cell-based gene therapy and immunotherapy of a number of diseases, including cancer (Naldini, 2015); and engineered plant viruses (such as tobacco mosaic virus and potato virus X) for the treatment of cancer in animal models (Czapar *et al.*, 2016; Shukla *et al.*, 2015). Exosomes have been hypothesized to be capable of transporting chemotherapeutic payloads to target tumours (Batrakova e Kim, 2015) due to their endogenous origin and organ-specific distribution. Finally, innovative inorganic NPs for the treatment of cancer, such as nanodiamond (Chow *et al.*, 2011; Mochalin *et al.*, 2013) and graphene (Jiang *et al.*, 2015; Liu *et al.*, 2008), have garnered a significant amount of attention.

In addition to this, there has already been significant innovation in the field of nanomedicine. Theranostic nanomedicine offers a promising strategy to monitor the PK and accumulation of therapeutics and the progression of disease. It does this by integrating diagnostic and therapeutic functions into a single NP formulation. This provides important insights into heterogeneities both within tumours and between patients for potential personalized treatment (Cheng *et al.*, 2012; Choi *et al.*, 2012). The huge number of *in vivo* examples demonstrates that nanoparticles could co-deliver numerous active pharmaceutical ingredients, which has allowed for the development of synergistic cancer treatments and circumvented certain mechanisms of drug resistance (Shi *et al.*, 2017). In addition to its use in the delivery of drugs, nanotechnology is making significant strides in the field of cancer immunotherapy. Increased tissue penetration and/or access to lymphatics, preferential uptake by antigen-presenting cells, sustained release of antigens or adjuvants, and NP-mediated phagosome escape of antigens for cross-presentation have made NPs increasingly attractive as potent antigen or adjuvant carriers for the development of synthetic vaccines (Cheng *et al.*, 2012; Irvine, Swartz e Szeto, 2013; Rosenthal *et al.*, 2014; Smith, Simon e Baker, 2013).

Nanotechnology will play a significant part in the achievement of the objective of early detection of cell populations that have undergone transformation by in vivo imaging or ex vivo analysis. It will also make it possible to select the appropriate combination of agents (based on accurate biological information regarding the tumour), to target these agents (while avoiding

biological barriers) to the early tumour lesions in order to eradicate or contain them without having any collateral effects on healthy tissue, and to monitor the treatment effect in real time.

5. ENCAPSULATION OF NSAIDs TARGETING CANCER

As was stated before, there is no question that NSAIDs and nanotechnology, both on their own, are two potential methods for the treatment of cancer. Thus, nanoencapsulation of NSAIDs can be expected to be an attractive strategy as a new cancer therapy, however, when we consider these concepts together, a variety of concerns are raised: What are the benefits of encapsulating NSAIDs? Is it even possible to do so, considering the limits of nanotechnology in cancer treatment right now? If nanoparticles were used, would NSAIDs still have their chemoprotective effect?

Because of their short half-lives and high protein binding affinities, NSAIDs require high drug dosages in order to have a successful chemoprotective effect. This leads to undesirable side effects, including complications with the digestive system and the cardiovascular system (Sostres *et al.*, 2010; Wongrakpanich *et al.*, 2018). Recent research has resulted in the development of NSAIDs based on nanomedicine in order to lessen the severity of these side effects.

5.1. Encapsulation of NSAIDs: anti-inflammatory nanomedicines

Poor aqueous solubility, low bioavailability, poor stability, bitter taste and unpleasant odour of some active agents are among the most encountered problems. Generally, encapsulation enables overcoming such obstacles. Encapsulation is an ingenious delivery opportunity for various drugs. For instance, it decreases systemic toxicity, protects unstable molecules from degradation in the gastrointestinal tract, provides controlled release properties, and masks the disagreeable taste of the drug. Controlled release, and targeted delivery enhance therapeutic efficacy compared to conventional medicine. The particle size and surface charge are the factors that can influence the release kinetics of nanomedecines (Arida e Al-Tabakha, 2007).

Encapsulation of NSAIDs is an interesting approach for their safe usage. Improvement of therapeutic efficacy and reduction in the severity of gastrointestinal side effects through modification of drug release can be considered in NSAIDs development. From the other hand, encapsulation would decrease the mucosal contact of NSAIDs, which are mostly weak acids consequently reduce the toxicity (Figueiredo, V., 2014). To promote the patient compliance, these formulations are designed by a change in their duration of action and plasma peak concentrations (Iqbal *et al.*, 2015; Phillips, Gran e Peppas, 2010; Rwei, Wang e Kohane, 2015).

In addition to the drug and materials physicochemical properties, the formulation of nanomedicine is associated to the selection of appropriate polymeric and lipidic systems giving enhanced bioavailability, retention time, and highest encapsulation efficiency (Table 2 and 3).

Table 2 - Encapsulated NSAIDs via polymer-based encapsulation techniques.

Method	Polymer	NSAIDs	Particle size (nm)	Zeta potential (mV)	Goal of encapsulation	Poly dispersity Index	EE (%)	Ref.
Nanoprecipitation	Eudragit RL 100	Aceclofenac	134.97	30.5	Prolongation of corneal contact time with drug	0.186	95.73	(Katara e Majumdar, 2013)
Nanoprecipitation	PCL	Nimesulide	344.6	-	Increasing of anti-inflammatory activity of topical nimesulide	0.251	-	(Lenz *et al.*, 2012)
Nanoprecipitation	Dextran	Ibuprofen	223.1	-50	Drug release adjustment	0.152	55.76	(Hornig, Bunjes e Heinze, 2009)
Emulsion-diffusion	PLC	Diclofenac	200	-	Attaining of colloidal system with good stability	-	-	(Mora-Huertas, Fessi e Elaissari, 2010)
Layer-by.layer	Sodium Alginate, Chitosan	Ketoprofen	41-111	-28 to -15	Obtaining prolonged release delivery system	-	-	(Arida e Al-Tabakha, 2007)
Double-emulsion solvent evaporation	Polymethylmethacrylate	Diclofenac sodium	215 µm	-	Drug release control	-	98.71	(Pal, Paul e Sa, 2011)
Emulsion-solvent evaporation	PLGA	Nimesulide	0.7 µm	-15 ± 3	Contributory treatment of prostate cancer	-	>83	(Huerta, Rosario Abertura s, del e Molpeceres, 2015)

EE: Entrapment effciency

Table 3 - NSAIDs encapsulated in liposomes, SLN and NLC.

Method	Active ingredient	Particle size (nm)	EE %	Poly dispersity index	Zeta potential (mV)	Goal of encapsulation	Ref.
Thin film hydration	Piroxicam	1660-66-76	12.5-36.6	0.28-1.00	-1.31 to -2,06	Functionalization of gauzes with liposomes entrapping an anti-inflammatory drug	(Ferreira *et al.*, 2013)
Thin lipid film hydration	Celecoxib	5450-6230	96.32	-	-	Design of celecoxib liposomal delivery system	(Deniz *et al.*, 2010)
Lipid hydration-extrusion	Indomethacin	150-200	93	0.069	-	Prevent the transfer of indomethacin across the placenta to the fetus	(Refuerzo *et al.*, 2015)
Hot homogenization	Indomethacin	140	72	0.16	-21	Development and characterization of Indomethacin-loaded solid lipid nanoparticles for occular drug delivery	(Hippalgaonkar *et al.*, 2013)
Microemulsion	Ketoprofen	75 ± 4	97	0.2	-15 to -17	Ketoprofen-loaded SLNs preparation by a mixture of beeswax and carnauba	(Kheradmandnia *et al.*, 2010)
Hot homogenization followed by sonication	Flubiprofen	250-350	>90	0.3-0-5	-21 to 42	Enhance oral bioavailability	(Bhaskar *et al.*, 2009)
Ultrasound	Flurbiprofen	288-459	92	0.245-0.639	-29.9 to -26.2	-	(Gonzalez-Mira *et al.*, 2010)
Hot melt homonization	Celecoxib	217	95	0.2	-25	Enhanced lung deposition time	(Patlolla *et al.*, 2010)

EE: Entrapment effciency

The various carriers that were loaded with NSAIDs and put through in vivo testing are detailed in Table 4. There has been research done on both nanoparticles and liposomes. Either rats or rabbits were used in the experiments for the study. In in vivo investigations, the ocular and intravenous administration routes were focused on the most frequently as potential points of administration targets. In addition, the topical, oral, and intranasal modes of administration were all utilized. Several outcomes, such as an increase in bioavailability, an improvement in drug accumulation at the targeted site, and prolonged release, have been validated. All the studies' tolerance was analysed, and the researchers concluded that the carriers under consideration did not pose any health risks. Flurbiprofen, diclofenac, indomethacin, and oxicams are among of the most prevalent active ingredients that have been investigated in vivo. It has also been demonstrated that encapsulated NSAIDs are more effective than normal dose forms. Liposomes, polymeric nanoparticles, and NLC are the three types of formulations that are most frequently researched. Considering these encouraging results, it would be fascinating to test encapsulated NSAIDs in human patients more thoroughly (Badri *et al.*, 2016).

Table 4 - Carriers already tested *in vivo*

Encapsulated NSAIDs	Carrier	Animal	Administration route	Study outcome	Ref.
Ibuprofen sodium	PEGylated gelatin nanoparticles	Sprague Dawley rats	Intravenous delivery	Improved plasma half-life of ibuprofen sodium	(Narayanan *et al.*, 2013)
Flurbiprofen	Nanostructured lipid carriers-based gel	Male Wistar rats	Skin delivery	-	(Han *et al.*, 2012)
Flurbiprofen	Nanostructured lipid carriers	Male albino rabbits	Ocular delivery	Ocular tolerance	(Gonzalez-Mira *et al.*, 2011)
Carprofen	PLGA nanoparticles	Male albino rabbits	Ocular delivery	Significant reduction of conjunctival inflammation and iris hyperemia compared to free drug	(Parra *et al.*, 2015)
Diclofenac	Liposomes	Albino rabbits	Ocular delivery	1.8-fold increase in diclofenac accumulation in the retina-choroid compared to aqueous solution	(Fujisawa *et al.*, 2012)
Diclofenac	Liposomes	Male Wistar rats	Intravenous delivery	Higher accumulation and prolonged retention at inflammation site	(Jukanti *et al.*, 2011)

Indomethacin	Liposomes	Male Wistar rats	Intravenous delivery	Enhanced bioavailability and local drug amount at inflammation site.	(Srinath *et al.*, 2000)
Meloxicam	Polymeric nanoparticles	Male Sprague Dawley rats	Nasal and oral delivery	Bioavailability enhancement	(Kürti *et al.*, 2013)
Piroxicam	Polymeric nanoparticles	Rabbits	Ocular delivery	More significant inhibition of inflammation than drug miocrosuspension	(Adibkia *et al.*, 2011)
Indomethacin	Polymeric nanoparticles	Albino rabbits	Ocular delivery	Increased active delivery to external and internal ocular tissues	(Badawi *et al.*, 2008)

Narayanan *et al*. created PEGylated gelatine nanoparticles containing ibuprofen with a particle size average of 200 nm (Narayanan *et al.*, 2013). When compared to free ibuprofen, ibuprofen-loaded nanoparticles that were delivered intravenously were able to effectively enhance the plasma half-life and improve drug bioavailability. In addition, a histological analysis of the kidney and liver indicated tissue integrity that was comparable to that of the control group, indicating the biocompatibility of the produced nanoparticles. In the same context, Shang et al. created a binary complex of EG950 and methacrylic acid hydrogel with Ibuprofen-loaded PLGA nanoparticles as a new intestine targeted drug delivery system for oral administration of ibuprofen (Shang *et al.*, 2017). This technology demonstrated the ability to distribute ibuprofen in a sustained-release way precisely to the alkaline environment of the intestine. This method improved the bioavailability of the medicine while simultaneously reducing the number of drug-related side effects.

Utilization of less toxic chemicals, economic scale-up through simplification of the technique, and optimization to improve yield and entrapment efficiency are the three pillars upon which the development of drug-loaded nanoparticles in the pharmaceutical industry is founded. The production of nanocapsules can be accomplished in several various ways by making use of polymers; the choice of a particular method is typically influenced by the physicochemical qualities of the medication, particularly the drug's solubility in water. Techniques that are risk-free, easy to follow, and easy to reproduce are currently available for the preparation of drug-loaded nanoparticles. The strategy that is selected for the preparation of the drug vehicle may have an impact on the nanocapsules that are manufactured. It is essential to bear in mind that the chosen procedure, when applied in accordance with the operational conditions, should not disrupt the stable state of the active ingredient. Because of

their unique physicochemical features, NSAIDs cannot be encapsulated using the same approach because they are all chemically classified as organic acids. In today's world, it is feasible to select the best method of preparation as well as the best polymer in order to accomplish an effective entrapping of the medication. This allows for the drug to be effectively contained. The technique that is used should result in a loss of the drug or its pharmacological action that is as small as possible. However, there are a few issues that need to be resolved. As a matter of fact, residual solvent analysis needs to be examined in more depth, and the post-preparative stages, including purification and preservation, which are especially crucial for nanocapsules, need to be optimized. Double-emulsion solvent evaporation, nanoprecipitation, and emulsion-solvent evaporation are the three technologies that are used the most frequently for encapsulating NSAIDs at the present time. Chitosan, poly(e-caprolactone), and Eudragit® are the most common types of polymers employed in the construction of sustained-release drug delivery systems. Most of the vehicles that were prepared were nanocarriers. The primary uses require promoted stability, prolonged release, and enhanced bioavailability. According to the current state of the art, ketoprofen was one of the first nonsteroidal anti-inflammatory drugs to be encapsulated (Badri *et al.*, 2016).

Molecules like indomethacin, nimesulide, acceclofenac, and celecoxib have been encapsulated in sulfonic acid relatively recently. According to the best of our knowledge, lipid-based carriers nanostructured lipid carriers (NLC) could be the best carrier for the delivery of NSAIDs in order to achieve various objectives such as gastrointestinal side effect reduction, solubility and bioavailability enhancement, stability increase, unpleasant taste cover, systemic toxicity reduction, and half-life control. These are just some of the goals that could be achieved. Ketoprofen, aceclofenac, and indomethacin are the NSAIDs that are encapsulated the most frequently. Notwithstanding this, most of the research on in vivo efficiency has been conducted on compounds such as flurbiprofen and diclofenac that have been specifically designed for ocular administration. The challenges of sustaining safety and tolerability, scaling up, and improving the quality of health service provision are the essential obstacles that need to be solved in order to have hope for a better tomorrow. Encapsulated NSAIDs are not yet available for purchase despite the intriguing success they have in testing on animals. In order to demonstrate the efficacy and safety of NSAIDs, studies have solely been conducted on animals up until this point. Because of this, it is essential to conduct additional investigations in human subjects in order to achieve successful therapeutic application of carriers in the relatively near future (Badri *et al.*, 2016).

5.2. Application of NSAIDs nanomedicines in cancer

The majority of NSAIDs have poor water solubility, bioavailability and have been linked to adverse effects on the gastrointestinal tract and the cardiovascular system, both of which have restricted their application in cancer treatment.

Several research groups have investigated aspirin's encapsulation and its efficacy in the treatment of cancer as part of an effort to enhance the pharmacokinetics of the drug using nanocarrier administration. In order to treat pancreatic cancer, Thakkar et al. co-loaded the antioxidant ferulic acid (FA) and the pain reliever aspirin into chitosan-coated solid lipid nanoparticles (c-SLNs). The results of the formulation optimization showed that c-SLNs of FA and aspirin exhibited suitable starting particle sizes in the range 183 ± 46 and 229 ± 67 nm, an encapsulation effectiveness of 80% and 78%, respectively, and zeta potentials of 39.1 and 50.3 mV, respectively. The research team discovered that each of the medications, when used on their own, had very little to no effect on the vitality of cancer cells; but, when the drugs were combined, they caused a viability decrease of approximately 70% (Thakkar *et al.*, 2015). Oral treatment of FA and aspirin co-loaded c-SLNs in pancreatic tumour xenograft mice model resulted in a growth suppression of 45% of the tumour in comparison to the control group, even though was not statistically significant. Furthermore, the pro-apoptotic role of the regimen was demonstrated by the immunohistochemical examination of tumour tissue, which revealed an increase in the expression of apoptotic proteins p-RB, p21, and p-ERK1/2, as well as a significant reduction in the expression of proliferation proteins PCNA and MKI67 (Thakkar *et al.*, 2015).

Ibuprofen is an easily accessible drug, but because to its poor pharmacokinetic qualities, its efficacy in vivo is insufficient. As a result, Cheng *et al.* examined the increased efficacy of phospho-ibuprofen amid (PIA)-loaded nanocarriers in a model of human lung tumours (Cheng *et al.*, 2014). When it came to suppressing the proliferation of human non-small cell lung cancer cells, PIA was found to be 10 times more effective than ibuprofen. A powerful cytokinetic impact is produced by PIA because of its ability to induce apoptosis, suppress cell proliferation, and prevent progression through the G0/G1 phase of the cell cycle. In addition, fluorescence imaging revealed that liposomal PIA *in vivo* significantly reduced the rate of growth of A549 xenografts by 95% ($p<0.001$) in comparison to the group that received the control vehicle. Ibuprofen was substantially less effective than the study drug, reducing tumour growth by almost half (55%). The study has proven that PIA can be loaded into liposomes in a very efficient manner, with a drug:lipid ratio of 1:1 When compared to ibuprofen's ability to

permeate cells in vitro, PIA's ability to do so was shown to be significantly superior due to its incorporation into liposomes. Based on the findings of in vivo biodistribution experiments, liposomal PIA was preferentially distributed to the lungs, resulting in higher levels than those in other organs (Cheng *et al.*, 2014). A study indicated that liposomes have the potential to change the biodistribution of paclitaxel (Wei *et al.*, 2014). This capability was demonstrated by the considerably increased delivery of the drug to the lungs by a factor of 14–20 in comparison to the delivery to other organs. As a result, the scientists advocated using liposomes as a potentially useful carrier to target the anticancer drug to the lungs in order to treat lung cancer. Because of the targeted delivery, intravenous injection of liposomal PIA needed just one-sixth of the dosage of free PIA that was free PIA dosage administered intravenously over the nearly total removal of the tumour. In addition, liposomes make it easier to target tumours thanks to a mechanism known as enhanced permeability and retention (EPR). This feature allows liposomes to extravasate via the "leaky" vasculature that is characteristic of tumours (Maeda *et al.*, 2000). These findings suggest that PIA, and particularly PIA that has been integrated into liposomes, is an effective inhibitor of lung cancer.

Ketoprofen is a COX inhibitor that isn't as well-known as some of the others, but it's still very common. Da Silveira *et al.* showed that treatment with ketoprofen-loaded nanocapsules (Keto-NC) reduced the viability glioma cells by 25% and 45%, respectively, after 48h and 72h of exposure (Silveira, Da *et al.*, 2013). In addition, treatment with keto-NC led to an increase in the permeability of the cell membrane, which is a marker of necrosis-induced cell death. It is important to note that the cytotoxicity caused by keto-NC was specific to gliomas, as the therapy had no effect on the viability of astrocyte cells. When compared to the control group, and the Keto-free solution group, the Keto-NC treatment resulted in a significant decrease in the volume of the glioma tumour. In addition, the results of the pathological examination revealed that Keto-NC was effective in lowering the malignant characteristic that is associated with a lower chance of survival and the worst prognosis for patients. It is important to note that Keto-NC did not raise mortality, nor did it cause systemic toxicity. In spite of the fact that it has a lot of potential, more research needs to be done in order to determine a therapeutic dose range and the toxicity of the Keto-NC formulation in different tumour animal models (Silveira, Da *et al.*, 2013).

The hallmarks of cancer, such as cell proliferation, evasion of apoptosis, and cell cycle regulation, can be influenced by NSAIDs, particularly aspirin (acetylsalicylic acid) and ibuprofen. In addition, inhibiting inflammatory mediators or signalling pathways that regulate inflammation reduces the number of tumours and slows the rate at which they grow, whereas increasing

levels of proinflammatory mediators or the adoptive transfer of inflammatory cells accelerates the development of tumours. It is only natural for these treatments to pique the curiosity of the scientific community, particularly considering the significant number of resources that are invested annually in cancer treatment. Considering this, a study was conducted to evaluate the effects of aspirin and ibuprofen, in bulk and nano forms, in peripheral lymphocytes of prostate cancer patients and healthy individuals (Guma *et al.*, 2021). In this research endeavour, two distinct forms of aspirin and ibuprofen were utilized, nano (ASP N and IBU N) and bulk (ASP B and IBU B). ASP N and IBU N presented an average size and zeta potential of 289 ± 3 nm, -6.1 mV and 323 ± 6.4 nm, -2.1 mV, respectively, indicating that the ibuprofen was more stable. Meanwhile, ASP B average particle size was 78.30 ± 0.23 μm and IBU B was 52.80 ± 4.37 μm. When compared to the untreated control group, lymphocytes from healthy donors that were subjected to exposure to ASP B, ASP N, IBU B and IBU N showed a significant decrease in the amount of DNA damage. It should be noted that only IBU N, ASP B, and ASP N induced a substantial reduction ($p< 0.01$, 0.01 and 0.001, respectively). The reduction of DNA damage caused by the nano form of both drugs examined was found to be higher than that caused by the bulk form. When compared to ASP B, the ASP N treatment resulted in a considerable reduction in the amount of DNA damage. In comparison to IBU B, the reduction in DNA damage caused by IBU N was shown to be significantly higher. When compared to the controls who were not given any treatment, the patients who had prostate cancer showed a substantial decrease in the amount of DNA damage with ASP B ($p<0.01$), ASP N ($p<0.001$), and IBU N ($p<0.01$) respectively. When compared to its bulk equivalent, the nano form of both aspirin and ibuprofen demonstrated a considerable reduction in the amount of DNA damage they caused. Ibuprofen's efficacy was surpassed, both in bulk and nano formulation, by the effectiveness of aspirin, which was the most effective drug (Guma *et al.*, 2021). The current study has showed that there is an improvement in activity when the particle size is dropped to the nano scale. This offers bioavailability without increasing the genetic toxicity when it is tested in vitro on human lymphocytes. Hence, this data on the genotoxicity mechanisms of NSAID in lymphocytes can shed fresh light on the ways in which cancer can be prevented and treated.

There is room for development in terms of the NSAIDs cancer-fighting capabilities. The anticancer activity of NSAIDs was improved by the development of a variety of different synthetic methods. The development of nanotechnology provided a new opportunity that can be exploited to improve the bioavailability of NSAIDs and the anticancer activity of these drugs by lowering the particle size of these drugs without altering their chemical structure. There

were some attempts made to nanoformulate NSAIDs (Badri *et al.*, 2016). For instance, when ibuprofen was delivered to breast cancer cells utilizing micelles as the carrier, a significant decrease in the cancer cells' viability was observed (Marques *et al.*, 2014). This research with functionalization of chitosan with deoxycholic acid and leucine moieties opened the door to the potential of engineering self-assembly delivery systems that efficiently encapsulate poorly water-soluble NSAIDs. Essentially, was demonstrated that it is possible to create a delivery system that is both highly biocompatible and reasonably affordable, and that this method can be utilized to successfully diminish the viability of breast cancer cells by delivering a commonly used NSAID (Marques *et al.*, 2014). A second study, in order to facilitate the administration of celecoxib for the purpose of treating colon cancer, used hydroxyapatite-chitosan nanocomposite (Venkatesan *et al.*, 2011). The nanoparticles demonstrated excellent encapsulation efficiency, sustained release patterns, optimal hemocompatibility, and increased cytotoxicity on colon cancer cells. The *in vivo* human colon tumour xenograft nude mice tumour investigations shown that the celecoxib-loaded hydroxyapatite-chitosan nanoparticles were more effective than free celecoxib in preventing the growth of tumours, and this method did not result in any severe adverse effects. Considering these findings, one can draw the conclusion that the hydroxyapatite-chitosan nanocomposite has the potential to serve as an efficient and risk-free vehicle for the administration of the chemotherapeutic drug celecoxib in the treatment of colon cancer. This preliminary strategy of nanoparticle-mediated targeted distribution might overcome negative effects produced by delivering unmodified celecoxib (Venkatesan *et al.*, 2011).

Bonelli *et al.* in order to combat the development of gastric cancer in humans, developed ibuprofen-loaded PLGA nanoparticles. The results shown, in comparison to cells that were treated with free ibuprofen at the same dose, a significant reduction in the proliferative ability of the cells that were treated with ibuprofen-loaded PLGA NPs. Ibuprofen started to be released rather quickly, during the first two hours, and then increased gradually over time, reaching its highest concentration after twenty-four hours. Additionally, the antiproliferative effects were seen even after 48 hours when no additional NPs were added. The fact that ibuprofen was found in the cell lysates led us to conclude that the NPs for the release it in the cells. It has been demonstrated on multiple occasions that the release of a therapeutic agent from PLGA NPs occurs in two phases. The first phase involves the diffusion of the therapeutic agent through the polymer matrix, while the second phase involves the diffusion of the therapeutic agent as well as the degradation of the polymer matrix itself. Using PLGA NPs as carriers, ibuprofen was able to exert an antiproliferative action at concentrations

that were over one hundred times lower than those of free ibuprofen. This indicates that the drug is more effective and causes less damage to the cells (Bonelli *et al.*, 2012).

In order to teste the anticancer activities of NSAIDs, nanodrugs loaded with naproxen, ibuprofen and ketoprofen were used in five different cell lines: human breast, pancreatic, colon, leukemia and ovarian cancer cell lines (Kumar, Siril e Javid, 2016). The effectiveness of the nanodrugs, raw-NSAIDs and raw-polymers was evaluated in comparison to that of the anticancer drug DOX, which is widely prescribed. Polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and hydroxypropyl methylcellulose (HPMC) are the three biocompatible and water-soluble polymers that were utilized in the process of stabilizing the drug nanoparticles. The findings make it abundantly clear that the majority of the nanoformulated NSAIDs shown an excellent level of anticancer activity against the leukemia cancer cell line. Unfortunately, in compared to the drug that is considered the gold standard, their anticancer effectiveness against other cancer cell lines that were tested is relatively low. When compared to ibuprofen and ketoprofen samples, naproxen samples had superior anti-leukemia activity. Naproxen in its nanoformulated form also demonstrated some anti-cancer potential against a human breast cancer cell line. Because their activity was superior to that of the standard drug, naproxen-HPMC and naproxen-PVP had excellent anti-leukemia action regardless of the concentration at which they were administered. Therefore, the activity of naproxen-PVP was over two times better than DOX. It's possible that zeta potential is the answer for the increased anti-leukemia action that was reported. Since raw naproxen and all nanoformulated NSAIDs have zeta potentials that are comparable to one another, whereas raw ibuprofen and raw ketoprofen have zeta potentials that are more in the negative. Can be drawn the conclusion that naproxen possesses strong anti-leukemia activity and that this activity has the potential to be increased through nanoformulation, in particular through the utilization of HPMC and PVP as polymeric stabilizers. To determine the exact mechanism underlying the observed improved anti-leukemia activity of the nanoformulated naproxen samples, additional research is required (Kumar, Siril e Javid, 2016).

Regardless of the level of COX expression present in the cell lines being tested, NSAIDs have been shown to exert both antiproliferative and apoptotic effects. Recent research (Motawi *et al.*, 2014) has demonstrated that naproxen can block the glycogen synthase kinase-3 beta (GSK-3β) pathway, which results in an increase in p53 cytosolic accumulation and inhibits the migration and survival of breast cancer cells. This pathway has been connected to the maintenance of CSCs (Domoto *et al.*, 2016), which suggests that naproxen may have a role to play as an adjuvant in chemotherapy. Previous findings have

shown that the use of naproxen and its derivatives may be able to improve the effectiveness of treatment for breast cancer (Deb *et al.*, 2014; Motawi *et al.*, 2014). Nevertheless, repeated administration of free forms of NAP are hindered by the drug's strong hydrophobicity, as well as by dose and time-dependent side effects on the GI tract (Ong *et al.*, 2007). In this context, nanomedicine presents the opportunity to increase the effectiveness of the free drugs and simultaneously decreasing the adverse effects of those drugs(Tran *et al.*, 2017). The most prevalent natural ligand for CD44, which is a widely recognised hallmark of CSC (Smith e Cai, 2012) and immune cells such macrophages (Mattheolabakis *et al.*, 2015; Rios de la Rosa *et al.*, 2017), is hyaluronic acid (HA). Therefore, by directly targeting this receptor, it is possible to obtain improved cellular absorption as well as selectivity towards immune cells and CSC. Due to its high binding affinity for the CD44 receptor, HA-based NPs have already been established to have the potential to be used as tumour site-specific medication delivery of anticancer drugs in breast cancer models (Kim *et al.*, 2018) and as anti-inflammatory treatments in inflammatory illnesses (Praveen Rao e Knaus, 2008). In a study conducted by Espinosa-Caro *et al.* focused at the development of HA-coated naproxen-based nanoparticles (HA-NPs) with enhanced CD44-mediated active-targeting ability and enhanced anti-cancer effects in comparison to free given naproxen (Espinosa-Cano *et al.*, 2021). The addition of HA coating improved the pH stability and hemocompatibility of the NP, provided better control over the esterase-dependent release of naproxen. In addition, as a direct result of the CD44 targeting, HA-coated NPs are faster and better internalized in CSC than they are in typical cancer cells that are not stem cells. This property, when combined with the anti-inflammatory activity of naproxen, makes HA-coating of poly(HNAP-co-VI)-based NPs an effective method for targeting CSC subpopulations within breast tumours. This can be accomplished either by directly attacking CSC or by preventing their occurrence as a result of a pro-inflammatory state. The technique also made it possible to lower the amount of naproxen that was administered to the luminal breast cancer cells in order to obtain the desired pro-apoptotic and anti-migratory activities. Moreover, the findings point to the possibility that the anti-cancer activity of NPs may be associated with the activation of apoptosis by means of modifications to GSK-3β-related COX-independent pathways. In conclusion, the NPs that have been produced are an excellent platform for the research and development of new anti-CSC medicines for the treatment of metastatic breast cancer (Espinosa-Cano *et al.*, 2021).

6. CONCLUSION

Given the intimate association that exists between inflammation and tumours, targeting inflammation is a crucial path to improve cancer treatment. Anti-inflammatory drugs offer a significant potential to be utilized both as adjuvants and as part of combination therapies. They are therefore an innovative therapeutic alternative that is less harmful to patients than the usual treatment approaches. Besides their already proven anticancer and chemoprotection effect (Wong, 2019), NSAIDs have well-established mechanism being an excellent option as next-generation cancer therapy. Nevertheless, these drugs have limited use due to side effects and toxicity, having the potential to become cumulative when they are taken for long periods of time as chemoprevention and treatment. In addition, poor water solubility and low bioavailability of NSAIDs make it necessary to adopt another strategy for these molecules have an increased efficacy in preventing and eliminating tumours (Guma *et al.*, 2021; Kumar, Siril e Javid, 2016).

Nanotechnology represents distinguish and functional approach to NSAIDs side effects, toxicity and physicochemical limitations, which restrict their application in cancer therapy. Using different nanoformulation techniques and drug delivery systems, encapsulated NSAIDs cause less side effects, had and enhance bioavailability and half-life, and are more effective than the free drug, thus, improving their efficacy as anticancer entities.

Nonetheless, despite the overwhelming evidence that NSAIDs, both free and nano-encapsulated, are effective against cancer, further research is still required. Overall, it's expected that soon more investment in NSAIDs-loaded nanocarriers are made since it's a very promising anticancer therapy.

7. REFERENCES

ADIBKIA, Khosro *et al.* - Naproxen–eudragit® RS100 nanoparticles: Preparation and physicochemical characterization. **Colloids and Surfaces B: Biointerfaces**. . ISSN 0927-7765. 83:1 (2011) 155–159. doi: https://doi.org/10.1016/j.colsurfb.2010.11.014.

AGGARWAL, Sanjeev *et al.* - Indomethacin-induced apoptosis in esophageal adenocarcinoma cells involves upregulation of bax and translocation of mitochondrial cytochrome C independent of COX-2 expression. **Neoplasia**. . ISSN 15228002. 2:4 (2000). doi: 10.1038/sj.neo.7900097.

ALI, Eunus S. *et al.* - Targeting cancer cells with nanotherapeutics and nanodiagnostics: Current status and future perspectives. **Seminars in cancer biology**. England. . ISSN 1096-3650

(Electronic). 69:2021) 52–68. doi: 10.1016/j.semcancer.2020.01.011.

ALSHAFIE, Galal A. *et al.* - Chemotherapeutic evaluation of Celecoxib, a cyclooxygenase-2 inhibitor, in a rat mammary tumor model. **Oncology Reports**. . ISSN 1021335X. 7:6 (2000). doi: 10.3892/or.7.6.1377.

AMITAY, Efrat L. *et al.* - Association of Aspirin and Nonsteroidal Anti-Inflammatory Drugs with Colorectal Cancer Risk by Molecular Subtypes. **Journal of the National Cancer Institute**. . ISSN 14602105. 111:5 (2019) 475–483. doi: 10.1093/jnci/djy170.

ARIDA, Adi I.; AL-TABAKHA, Moawia M. - Encapsulation of ketoprofen for controlled drug release. **European Journal of Pharmaceutics and Biopharmaceutics**. . ISSN 0939-6411. 66:1 (2007) 48–54. doi: https://doi.org/10.1016/j.ejpb.2006.09.010.

ASHTON, Susan *et al.* - Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index in vivo. **Science Translational Medicine**. . ISSN 19466242. 8:325 (2016). doi: 10.1126/scitranslmed.aad2355.

BADAWI, Alia A. *et al.* - Chitosan based nanocarriers for indomethacin ocular delivery. **Archives of Pharmacal Research**. . ISSN 1976-3786. 31:8 (2008) 1040–1049. doi: 10.1007/s12272-001-1266-6.

BADRI, Waisudin *et al.* - Encapsulation of NSAIDs for inflammation management: Overview, progress, challenges and prospects. **International Journal of Pharmaceutics**. . ISSN 18733476. 515:1–2 (2016). doi: 10.1016/j.ijpharm.2016.11.002.

BALKWILL, Fran; MANTOVANI, Alberto - Inflammation and cancer: Back to Virchow? **Lancet**. . ISSN 01406736. 357:9255 (2001). doi: 10.1016/S0140-6736(00)04046-0.

BARENHOLZ, Yechezkel - Doxil® - The first FDA-approved nano-drug: Lessons learned. **Journal of Controlled Release**. . ISSN 01683659. 160:2 (2012). doi: 10.1016/j.jconrel.2012.03.020.

BARNARD, Mollie E. *et al.* - Association of Analgesic Use With Risk of Ovarian Cancer in the Nurses' Health Studies. **JAMA Oncology**. . ISSN 23742445. 4:12 (2018) 1675–1682. doi: 10.1001/jamaoncol.2018.4149.

BASTIAANNET, E. *et al.* - Use of Aspirin postdiagnosis improves survival for colon cancer patients. **British Journal of Cancer**. . ISSN 00070920. 106:9 (2012) 1564–1570. doi: 10.1038/bjc.2012.101.

BATRAKOVA, Elena V.; KIM, Myung Soo - Using exosomes, naturally-equipped nanocarriers,

for drug delivery. **Journal of Controlled Release**. . ISSN 18734995. 219:2015). doi: 10.1016/j.jconrel.2015.07.030.

BENS, Annet *et al.* - Nonaspirin NSAIDs and contralateral breast cancer risk. **International Journal of Cancer**. . ISSN 10970215. 144:6 (2019) 1243–1250. doi: 10.1002/ijc.31949.

BHASKAR, Kesavan *et al.* - Lipid nanoparticles for transdermal delivery of flurbiprofen: formulation, in vitro, ex vivo and in vivo studies. **Lipids in Health and Disease**. . ISSN 1476-511X. 8:1 (2009) 6. doi: 10.1186/1476-511X-8-6.

BONELLI, Patrizia *et al.* - Ibuprofen delivered by poly(lactic-co-glycolic acid) (PLGA) nanoparticles to human gastric cancer cells exerts antiproliferative activity at very low concentrations. **International Journal of Nanomedicine**. . ISSN 11769114. 7:2012). doi: 10.2147/IJN.S34723.

BRADLEY, M. C. *et al.* - Non-steroidal anti-inflammatory drugs and pancreatic cancer risk: A nested case-control study. **British Journal of Cancer**. . ISSN 00070920. 102:9 (2010) 1415–1421. doi: 10.1038/sj.bjc.6605636.

BRASKY, Theodore M. *et al.* - Non-steroidal anti-inflammatory drugs (NSAIDs) and breast cancer risk: Differences by molecular subtype. **Cancer Causes and Control**. . ISSN 09575243. 22:7 (2011). doi: 10.1007/s10552-011-9769-9.

BRASKY, Theodore M. *et al.* - Non-steroidal anti-inflammatory drugs and cancer risk in women: Results from the Women's Health Initiative. **International Journal of Cancer**. . ISSN 10970215. 135:8 (2014) 1869–1883. doi: 10.1002/ijc.28823.

CAI, Ting Ting *et al.* - LMP1-mediated glycolysis induces myeloid-derived suppressor cell expansion in nasopharyngeal carcinoma. **PLoS Pathogens**. . ISSN 15537374. 13:7 (2017). doi: 10.1371/journal.ppat.1006503.

CAIRAT, Manon *et al.* - Antiplatelet drug use and breast cancer risk in a prospective cohort of postmenopausal women. **Cancer Epidemiology Biomarkers and Prevention**. . ISSN 15387755. 30:4 (2021) 643–652. doi: 10.1158/1055-9965.EPI-20-1292.

CAO, Yin *et al.* - Population-wide impact of long-term use of aspirin and the risk for cancer. **JAMA Oncology**. . ISSN 23742445. 2:6 (2016). doi: 10.1001/jamaoncol.2015.6396.

CELATOR PHARMACEUTICALS, Inc - Celator announces phase 3 trial for VYXEOS™ (CPX-351) in patients with high-risk acute myeloid leukemia demonstrates statistically significant improvement in overall survival. **prnewswire**. 2016).

CHAN, Timothy A. *et al.* - Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. **Proceedings of the National Academy of Sciences of the United States of America**. . ISSN 00278424. 95:2 (1998). doi: 10.1073/pnas.95.2.681.

CHARALAMBOUS, M. P. *et al.* - Upregulation of cyclooxygenase-2 is accompanied by increased expression of nuclear factor-κB and IκB kinase-α in human colorectal cancer epithelial cells. **British Journal of Cancer**. . ISSN 00070920. 88:10 (2003). doi: 10.1038/sj.bjc.6600927.

CHEN, Enrui *et al.* - Mechanism investigation of hyaluronidase-combined multistage nanoparticles for solid tumor penetration and antitumor effect. **International Journal of Nanomedicine**. . ISSN 11782013. 15:2020). doi: 10.2147/IJN.S257164.

CHEN, Xuechen *et al.* - Non-steroidal anti-inflammatory drugs, polygenic risk score and colorectal cancer risk. **Alimentary Pharmacology and Therapeutics**. . ISSN 13652036. 54:2 (2021) 167–175. doi: 10.1111/apt.16438.

CHEN, Yongyan; TIAN, Zhigang - HBV-induced immune imbalance in the development of HCC. **Frontiers in Immunology**. . ISSN 16643224. 10:AUG (2019). doi: 10.3389/fimmu.2019.02048.

CHENG, Ka Wing *et al.* - A novel ibuprofen derivative with anti-lung cancer properties: Synthesis, formulation, pharmacokinetic and efficacy studies. **International Journal of Pharmaceutics**. . ISSN 18733476. 477:1–2 (2014). doi: 10.1016/j.ijpharm.2014.10.019.

CHENG, Zhe *et al.* - Nanomaterials for cancer therapy: current progress and perspectives. **Journal of Hematology & Oncology**. . ISSN 1756-8722. 14:1 (2021) 85. doi: 10.1186/s13045-021-01096-0.

CHENG, Zhiliang *et al.* - Multifunctional nanoparticles: Cost versus benefit of adding targeting and imaging capabilities. **Science**. . ISSN 10959203. 338:6109 (2012). doi: 10.1126/science.1226338.

CHO, Kwangjae *et al.* - Therapeutic nanoparticles for drug delivery in cancer. **Clinical Cancer Research**. . ISSN 10780432. 14:5 (2008). doi: 10.1158/1078-0432.CCR-07-1441.

CHOI, Ki Young *et al.* - Theranostic nanoplatforms for simultaneous cancer imaging and therapy: Current approaches and future perspectives. **Nanoscale**. . ISSN 20403364. 4:2 (2012). doi: 10.1039/c1nr11277e.

CHOW, Edward K. *et al.* - Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment. **Science Translational Medicine**. . ISSN 19466234. 3:73

(2011). doi: 10.1126/scitranslmed.3001713.

CLARKE, Christina A. *et al.* - Regular and low-dose aspirin, other non-steroidal anti-inflammatory medications and prospective risk of HER2-defined breast cancer: The California Teachers Study. **Breast Cancer Research**. . ISSN 1465542X. 19:1 (2017) 1–12. doi: 10.1186/s13058-017-0840-7.

COGHILL, Anna E. *et al.* - The association between NSAID use and colorectal cancer mortality: Results from the women's health initiative. **Cancer Epidemiology Biomarkers and Prevention**. . ISSN 10559965. 21:11 (2012) 1966–1973. doi: 10.1158/1055-9965.EPI-12-0672.

CONDEELIS, John; POLLARD, Jeffrey W. - Macrophages: Obligate partners for tumor cell migration, invasion, and metastasis. **Cell**. . ISSN 00928674. 124:2 (2006). doi: 10.1016/j.cell.2006.01.007.

CORRALES, Leticia *et al.* - Innate immune signaling and regulation in cancer immunotherapy. **Cell Research**. . ISSN 1748-7838. 27:1 (2017) 96–108. doi: 10.1038/cr.2016.149.

COUSSENS, Lisa M.; WERB, Zena - Inflammation and cancer. **Nature**. . ISSN 1476-4687. 420:6917 (2002) 860–867. doi: 10.1038/nature01322.

CRONIN-FENTON, Deirdre P. *et al.* - Prescriptions for selective cyclooxygenase-2 inhibitors, non-selective non-steroidal anti-inflammatory drugs, and risk of breast cancer in a population-based case-control study. **Breast Cancer Research**. . ISSN 14655411. 12:2 (2010) 27–30. doi: 10.1186/bcr2482.

CRUSZ, Shanthini M.; BALKWILL, Frances R. - Inflammation and cancer: Advances and new agents. **Nature Reviews Clinical Oncology**. . ISSN 17594782. 12:10 (2015). doi: 10.1038/nrclinonc.2015.105.

CZAPAR, Anna E. *et al.* - Tobacco Mosaic Virus Delivery of Phenanthriplatin for Cancer therapy. **ACS Nano**. . ISSN 1936086X. 10:4 (2016). doi: 10.1021/acsnano.5b07360.

DAS, Ujjal *et al.* - Radiosensitizing effect of ellagic acid on growth of Hepatocellular carcinoma cells: An in vitro study. **Scientific Reports**. . ISSN 20452322. 7:1 (2017). doi: 10.1038/s41598-017-14211-4.

DAVIS, Mark E. *et al.* - Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. **Nature**. . ISSN 1476-4687 (Electronic). 464:7291 (2010) 1067–1070. doi: 10.1038/nature08956.

DAWSON, Mark A.; KOUZARIDES, Tony - Cancer epigenetics: from mechanism to therapy. **Cell**. United States. . ISSN 1097-4172 (Electronic). 150:1 (2012) 12–27. doi: 10.1016/j.cell.2012.06.013.

DENIZ, Asli *et al.* - Celecoxib-loaded liposomes: Effect of cholesterol on encapsulation and in vitro release characteristics. **Bioscience Reports**. . ISSN 01448463. 30:5 (2010). doi: 10.1042/BSR20090104.

DIERSSEN-SOTOS, Trinidad *et al.* - Use of non-steroidal anti-inflammatory drugs and risk of breast cancer: The Spanish Multi-Case-control (MCC) study. **BMC Cancer**. . ISSN 14712407. 16:1 (2016). doi: 10.1186/s12885-016-2692-4.

DIN, Farhat V. N. *et al.* - Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. **Gut**. . ISSN 00175749. 59:12 (2010) 1670–1679. doi: 10.1136/gut.2009.203000.

DOAT, Solene *et al.* - Nonsteroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk: results from the EPICAP study. **Cancer medicine**. . ISSN 2045-7634 (Electronic). 6:10 (2017) 2461–2470. doi: 10.1002/cam4.1186.

DONG, Xiao-Feng *et al.* - COX-2/PGE2 Axis Regulates HIF2α Activity to Promote Hepatocellular Carcinoma Hypoxic Response and Reduce the Sensitivity of Sorafenib Treatment. **Clinical cancer research : an official journal of the American Association for Cancer Research**. United States. . ISSN 1557-3265 (Electronic). 24:13 (2018) 3204–3216. doi: 10.1158/1078-0432.CCR-17-2725.

DOWNER, Mary K. *et al.* - Aspirin Use and Lethal Prostate Cancer in the Health Professionals Follow-up Study. **European Urology Oncology**. . ISSN 25889311. 2:2 (2019) 126–134. doi: 10.1016/j.euo.2018.07.002.

DRITSCHILO, Anatoly *et al.* - Phase I study of liposome-encapsulated c-raf antisense oligodeoxyribonucleotide infusion in combination with radiation therapy in patients with advanced malignancies. **Clinical Cancer Research**. . ISSN 10780432. 12:4 (2006). doi: 10.1158/1078-0432.CCR-05-1260.

ELAZAR, Victoria *et al.* - Sustained delivery and efficacy of polymeric nanoparticles containing osteopontin and bone sialoprotein antisenses in rats with breast cancer bone metastasis. **International Journal of Cancer**. . ISSN 00207136. 126:7 (2010). doi: 10.1002/ijc.24890.

ELIASSEN, A. Heather *et al.* - Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and risk of breast cancer among premenopausal women in the nurses' health study II. **Archives of Internal Medicine**. . ISSN 00039926. 169:2 (2009). doi:

10.1001/archinternmed.2008.537.

ESBONA, Karla *et al.* - The Presence of Cyclooxygenase 2, Tumor-Associated Macrophages, and Collagen Alignment as Prognostic Markers for Invasive Breast Carcinoma Patients. **American Journal of Pathology**. . ISSN 15252191. 188:3 (2018). doi: 10.1016/j.ajpath.2017.10.025.

FERREIRA, Helena *et al.* - Functionalization of gauzes with liposomes entrapping an anti-inflammatory drug: A strategy to improve wound healing. **Reactive and Functional Polymers**. . ISSN 1381-5148. 73:10 (2013) 1328–1334. doi: https://doi.org/10.1016/j.reactfunctpolym.2013.05.012.

FIGUEIREDO, Catarina Pinto Reis V. - Ibuprofen Nanoparticles for Oral Delivery: Proof of Concept. **Journal of Nanomedicine & Biotherapeutic Discovery**. 04:01 (2014). doi: 10.4172/2155-983x.1000119.

FLETCHER, Rochelle *et al.* - Non-steroidal anti-inflammatory drugs induce immunogenic cell death in suppressing colorectal tumorigenesis. **Oncogene**. . ISSN 14765594. 40:11 (2021) 2035–2050. doi: 10.1038/s41388-021-01687-8.

FRIIS, Søren *et al.* - Low-Dose Aspirin or Nonsteroidal Anti-inflammatory Drug Use and Colorectal Cancer Risk. **Annals of Internal Medicine**. . ISSN 0003-4819. 163:5 (2015). doi: 10.7326/m15-0039.

FUJISAWA, Takuya *et al.* - Liposomal diclofenac eye drop formulations targeting the retina: Formulation stability improvement using surface modification of liposomes. **International Journal of Pharmaceutics**. . ISSN 0378-5173. 436:1 (2012) 564–567. doi: https://doi.org/10.1016/j.ijpharm.2012.07.024.

FUJITA, Hiroshi *et al.* - Cyclooxygenase-2 promotes prostate cancer progression. **Prostate**. . ISSN 02704137. 53:3 (2002) 232–240. doi: 10.1002/pros.10152.

GAJEWSKI, Thomas F.; SCHREIBER, Hans; FU, Yang-Xin - Innate and adaptive immune cells in the tumor microenvironment. **Nature Immunology**. . ISSN 1529-2916. 14:10 (2013) 1014–1022. doi: 10.1038/ni.2703.

GHANGHAS, Preety *et al.* - Chemopreventive action of non-steroidal anti-inflammatory drugs on the inflammatory pathways in colon cancer. **Biomedicine and Pharmacotherapy**. . ISSN 19506007. 78:2016) 239–247. doi: 10.1016/j.biopha.2016.01.024.

GONZALEZ-MIRA, E. *et al.* - Optimizing flurbiprofen-loaded {NLC} by central composite factorial design for ocular delivery. **Nanotechnology**. 22:4 (2010) 45101. doi: 10.1088/0957-

4484/22/4/045101.

GONZALEZ-MIRA, E. *et al.* - Optimizing flurbiprofen-loaded NLC by central composite factorial design for ocular delivery. **Nanotechnology**. . ISSN 09574484. 22:4 (2011). doi: 10.1088/0957-4484/22/4/045101.

GOTTLIEB, Michael; NAKITENDE, Damali - Comparison of tamsulosin, nifedipine, and placebo for ureteric colic. **Canadian Journal of Emergency Medicine**. . ISSN 14818043. 19:2 (2017). doi: 10.1017/cem.2015.105.

GRADISHAR, William J. *et al.* - Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. **Journal of Clinical Oncology**. . ISSN 0732183X. 23:31 (2005). doi: 10.1200/JCO.2005.04.937.

GREENHOUGH, Alexander *et al.* - The COX-2/PGE2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. **Carcinogenesis**. England. . ISSN 1460-2180 (Electronic). 30:3 (2009) 377–386. doi: 10.1093/carcin/bgp014.

GRIVENNIKOV, Sergei I.; GRETEN, Florian R.; KARIN, Michael - Immunity, Inflammation, and Cancer. **Cell**. . ISSN 0092-8674. 140:6 (2010) 883–899. doi: https://doi.org/10.1016/j.cell.2010.01.025.

GRIVENNIKOV, Sergei I.; KARIN, Michael - Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer. **Cytokine & growth factor reviews**. . ISSN 1879-0305 (Electronic). 21:1 (2010) 11–19. doi: 10.1016/j.cytogfr.2009.11.005.

GRIVENNIKOV, Sergei I.; KARIN, Michael - Inflammatory cytokines in cancer: Tumour necrosis factor and interleukin 6 take the stage. **Annals of the Rheumatic Diseases**. . ISSN 00034967. 70:SUPPL. 1 (2011). doi: 10.1136/ard.2010.140145.

GUMA, Azeza *et al.* - Ex vivo/in vitro effects of aspirin and ibuprofen, bulk and nano forms, in peripheral lymphocytes of prostate cancer patients and healthy individuals. **Mutation Research - Genetic Toxicology and Environmental Mutagenesis**. . ISSN 18793592. 861–862:2021). doi: 10.1016/j.mrgentox.2020.503306.

GUPTA, Subash Chandra *et al.* - Inflammation, a Double-Edge Sword for Cancer and Other Age-Related Diseases. **Frontiers in Immunology**. . ISSN 16643224. 9:2018). doi: 10.3389/fimmu.2018.02160.

GURPINAR, Evrim; GRIZZLE, William E.; PIAZZA, Gary A. - NSAIDs inhibit tumorigenesis, but how? **Clinical Cancer Research**. . ISSN 15573265. 20:5 (2014). doi: 10.1158/1078-0432.CCR-13-1573.

GUTHRIE, Graeme J. K. *et al.* - The systemic inflammation-based neutrophil-lymphocyte ratio: Experience in patients with cancer. **Critical Reviews in Oncology/Hematology**. . ISSN 10408428. 88:1 (2013). doi: 10.1016/j.critrevonc.2013.03.010.

HAN, Fei *et al.* - Nanostructured lipid carriers (NLC) based topical gel of flurbiprofen: Design, characterization and in vivo evaluation. **International Journal of Pharmaceutics**. . ISSN 0378-5173. 439:1 (2012) 349–357. doi: https://doi.org/10.1016/j.ijpharm.2012.08.040.

HANAHAN, Douglas; WEINBERG, Robert A. - Hallmarks of cancer: the next generation. **Cell**. United States. . ISSN 1097-4172 (Electronic). 144:5 (2011) 646–674. doi: 10.1016/j.cell.2011.02.013.

HAO, Yibin *et al.* - Establishment of optimal regulatory network of colorectal cancer based on p42.3 protein. **Saudi Journal of Biological Sciences**. . ISSN 1319562X. 24:8 (2017). doi: 10.1016/j.sjbs.2017.11.012.

HARRIS, Randall E. *et al.* - Breast cancer and nonsteroidal anti-inflammatory drugs: Prospective results from the Women's Health Initiative. **Cancer Research**. . ISSN 00085472. 63:18 (2003).

HASHEMI GORADEL, Nasser *et al.* - Cyclooxygenase-2 in cancer: A review. **Journal of Cellular Physiology**. 234:5 (2019) 5683–5699. doi: https://doi.org/10.1002/jcp.27411.

HIBINO, Sana *et al.* - Inhibition of Nr4a Receptors Enhances Antitumor Immunity by Breaking Treg-Mediated Immune Tolerance. **Cancer research**. United States. . ISSN 1538-7445 (Electronic). 78:11 (2018) 3027–3040. doi: 10.1158/0008-5472.CAN-17-3102.

HINGORANI, Sunil R. *et al.* - Phase Ib study of PEGylated recombinant human hyaluronidase and gemcitabine in patients with advanced pancreatic cancer. **Clinical Cancer Research**. . ISSN 15573265. 22:12 (2016). doi: 10.1158/1078-0432.CCR-15-2010.

HIPPALGAONKAR, Ketan *et al.* - Indomethacin-Loaded Solid Lipid Nanoparticles for Ocular Delivery: Development, Characterization, and In Vitro Evaluation. **Journal of Ocular Pharmacology and Therapeutics**. 29:2 (2013) 216–228. doi: 10.1089/jop.2012.0069.

HÖING, Benedikt *et al.* - Stromal versus tumoral inflammation differentially contribute to metastasis and poor survival in laryngeal squamous cell carcinoma. **Oncotarget**. . ISSN 19492553. 9:9 (2018). doi: 10.18632/oncotarget.23865.

HORNIG, Stephanie; BUNJES, Heike; HEINZE, Thomas - Preparation and characterization of nanoparticles based on dextran–drug conjugates. **Journal of Colloid and Interface Science**. . ISSN 0021-9797. 338:1 (2009) 56–62. doi:

https://doi.org/10.1016/j.jcis.2009.05.025.

HOSSEINI, Fatemeh *et al.* - Anti-inflammatory and anti-tumor effects of α-L-guluronic acid (G2013) on cancer-related inflammation in a murine breast cancer model. **Biomedicine and Pharmacotherapy**. . ISSN 19506007. 98:2018). doi: 10.1016/j.biopha.2017.12.111.

HOU, Pei Chi *et al.* - Hypoxia-induced downregulation of DUSP-2 phosphatase drives colon cancer stemness. **Cancer Research**. . ISSN 15387445. 77:16 (2017). doi: 10.1158/0008-5472.CAN-16-2990.

HUERTA, Concepción; ROSARIO ABERTURAS, María DEL; MOLPECERES, Jesús - Nimesulide-loaded nanoparticles for the potential coadjuvant treatment of prostate cancer. **International Journal of Pharmaceutics**. . ISSN 0378-5173. 493:1 (2015) 152–160. doi: https://doi.org/10.1016/j.ijpharm.2015.07.027.

HUNG, Jui Hsiang *et al.* - Endoplasmic reticulum stress stimulates the expression of cyclooxygenase-2 through activation of NF-κB and pp38 mitogen-activated protein kinase. **Journal of Biological Chemistry**. . ISSN 00219258. 279:45 (2004). doi: 10.1074/jbc.M403568200.

HURWITZ, Lauren M. *et al.* - Aspirin and non-aspirin NSAID use and prostate cancer incidence, mortality, and case fatality in the Atherosclerosis Risk in Communities study. **Cancer Epidemiology Biomarkers and Prevention**. . ISSN 10559965. 28:3 (2019) 563–569. doi: 10.1158/1055-9965.EPI-18-0965.

INMAN, Silas. - FDA Approves Second-Line MM-398 Regimen for Metastatic Pancreatic Cancer. **Onclive**. 2015).

IQBAL, Muhammad *et al.* - Double emulsion solvent evaporation techniques used for drug encapsulation. **International Journal of Pharmaceutics**. . ISSN 0378-5173. 496:2 (2015) 173–190. doi: https://doi.org/10.1016/j.ijpharm.2015.10.057.

IRVINE, Darrell J.; SWARTZ, Melody A.; SZETO, Gregory L. - Engineering synthetic vaccines using cues from natural immunity. **Nature Materials**. . ISSN 14764660. 12:11 (2013). doi: 10.1038/nmat3775.

ISLAM, Mohammad Ariful *et al.* - Biomaterials for mRNA delivery. **Biomaterials Science**. . ISSN 20474849. 3:12 (2015). doi: 10.1039/c5bm00198f.

JACOBS, Eric J. *et al.* - A large cohort study of long-term acetaminophen use and prostate cancer incidence. **Cancer Epidemiology Biomarkers and Prevention**. . ISSN 10559965. 20:7 (2011) 1322–1328. doi: 10.1158/1055-9965.EPI-11-0210.

JENSEN, Samuel A. *et al.* - Spherical nucleic acid nanoparticle conjugates as an RNAi-based therapy for glioblastoma. **Science Translational Medicine**. . ISSN 19466234. 5:209 (2013). doi: 10.1126/scitranslmed.3006839.

JEONG, Kyeongsoo *et al.* - Exosome-mediated microRNA-497 delivery for anti-cancer therapy in a microfluidic 3D lung cancer model. **Lab on a Chip**. . ISSN 14730189. 20:3 (2020). doi: 10.1039/c9lc00958b.

JESS, Tine *et al.* - Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. **Gastroenterology**. . ISSN 15280012. 143:2 (2012). doi: 10.1053/j.gastro.2012.04.016.

JIANG, Tianyue *et al.* - Furin-mediated sequential delivery of anticancer cytokine and small-molecule drug shuttled by graphene. **Advanced Materials**. . ISSN 15214095. 27:6 (2015). doi: 10.1002/adma.201404498.

JUKANTI, Raju *et al.* - Drug targeting to inflammation: Studies on antioxidant surface loaded diclofenac liposomes. **International Journal of Pharmaceutics**. . ISSN 0378-5173. 414:1 (2011) 179–185. doi: https://doi.org/10.1016/j.ijpharm.2011.05.031.

KANDA, Akio *et al.* - Loxoprofen sodium suppresses mouse tumor growth by inhibiting vascular endothelial growth factor. **Acta oncologica (Stockholm, Sweden)**. England. . ISSN 0284-186X (Print). 42:1 (2003) 62–70. doi: 10.1080/0891060310002258.

KARIN, Michael - The IkappaB kinase - a bridge between inflammation and cancer. **Cell research**. England. . ISSN 1748-7838 (Electronic). 18:3 (2008) 334–342. doi: 10.1038/cr.2008.30.

KATARA, Rajesh; MAJUMDAR, Dipak K. - Eudragit RL 100-based nanoparticulate system of aceclofenac for ocular delivery. **Colloids and Surfaces B: Biointerfaces**. . ISSN 0927-7765. 103:2013) 455–462. doi: https://doi.org/10.1016/j.colsurfb.2012.10.056.

KE, Jieqi *et al.* - Prostaglandin E2 (PGE2) promotes proliferation and invasion by enhancing SUMO-1 activity via EP4 receptor in endometrial cancer. **Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine**. . ISSN 1423-0380 (Electronic). 37:9 (2016) 12203–12211. doi: 10.1007/s13277-016-5087-x.

KEARNEY, Cathal J.; MOONEY, David J. - Macroscale delivery systems for molecular and cellular payloads. **Nature Materials**. . ISSN 14761122. 12:11 (2013). doi: 10.1038/nmat3758.

KEHM, Rebecca D. *et al.* - Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or genetic risk: A cohort study. **Breast**

Cancer Research. . ISSN 1465542X. 21:1 (2019) 1–13. doi: 10.1186/s13058-019-1135-y.

KELLER, D. S. *et al.* - Colorectal cancer in inflammatory bowel disease: review of the evidence. **Techniques in Coloproctology**. . ISSN 1128-045X. 23:1 (2019) 3–13. doi: 10.1007/s10151-019-1926-2.

KHERADMANDNIA, Soheila *et al.* - Preparation and characterization of ketoprofen-loaded solid lipid nanoparticles made from beeswax and carnauba wax. **Nanomedicine: Nanotechnology, Biology and Medicine**. . ISSN 1549-9634. 6:6 (2010) 753–759. doi: https://doi.org/10.1016/j.nano.2010.06.003.

KHUDER, Sadik A. *et al.* - Nonsteroidal antiinflammatory drug use and lung cancer: A metaanalysis. **Chest**. . ISSN 00123692. 127:3 (2005) 748–754. doi: 10.1378/chest.127.3.748.

KIM, Sangmi *et al.* - Lifetime use of nonsteroidal anti-inflammatory drugs and breast cancer risk: Results from a prospective study of women with a sister with breast cancer. **BMC Cancer**. . ISSN 14712407. 15:1 (2015). doi: 10.1186/s12885-015-1979-1.

KIRSH, Victoria A. *et al.* - Nonsteroidal antiinflammatory drug use and breast cancer risk: Subgroup findings. **American Journal of Epidemiology**. . ISSN 00029262. 166:6 (2007) 709–716. doi: 10.1093/aje/kwm216.

KO, C. J. *et al.* - Inhibition of cyclooxygenase-2-mediated matriptase activation contributes to the suppression of prostate cancer cell motility and metastasis. **Oncogene**. . ISSN 14765594. 36:32 (2017). doi: 10.1038/onc.2017.82.

KUJAWSKI, Maciej *et al.* - Stat3 mediates myeloid cell-dependent tumor angiogenesis in mice. **The Journal of clinical investigation**. . ISSN 0021-9738 (Print). 118:10 (2008) 3367–3377. doi: 10.1172/JCI35213.

KUMAR, Raj; SIRIL, Prem Felix; JAVID, Farideh - Unusual anti-leukemia activity of nanoformulated naproxen and other non-steroidal anti-inflammatory drugs. **Materials Science and Engineering C**. . ISSN 09284931. 69:2016). doi: 10.1016/j.msec.2016.08.024.

KÜRTI, Levente *et al.* - In vitro and in vivo characterization of meloxicam nanoparticles designed for nasal administration. **European Journal of Pharmaceutical Sciences**. . ISSN 0928-0987. 50:1 (2013) 86–92. doi: https://doi.org/10.1016/j.ejps.2013.03.012.

LANG, S. *et al.* - COX-inhibitors relieve the immunosuppressive effect of tumor cells and improve functions of immune effectors. **International Journal of Immunopathology and Pharmacology**. . ISSN 03946320. 19:2 (2006). doi: 10.1177/039463200601900217.

LENZ, Quéli Fernandes *et al.* - Semi-solid topical formulations containing nimesulide-loaded nanocapsules showed in-vivo anti-inflammatory activity in chronic arthritis and fibrovascular tissue models. **Inflammation Research**. . ISSN 1420-908X. 61:4 (2012) 305–310. doi: 10.1007/s00011-011-0411-9.

LI, Yanli *et al.* - Use of nonsteroidal anti-inflammatory drugs and survival following breast cancer diagnosis. **Cancer Epidemiology Biomarkers and Prevention**. . ISSN 10559965. 21:1 (2012) 239–242. doi: 10.1158/1055-9965.EPI-11-1012.

LIU, Zhuang *et al.* - PEGylated nanographene oxide for delivery of water-insoluble cancer drugs. **Journal of the American Chemical Society**. . ISSN 1520-5126 (Electronic). 130:33 (2008) 10876–10877. doi: 10.1021/ja803688x.

LOOR, Alexandra; DUMITRAȘCU, D. L. - Helicobacter pylori Infection, Gastric Cancer and Gastropanel. **Romanian journal of internal medicine = Revue roumaine de medecine interne**. . ISSN 12204749. 54:3 (2016). doi: 10.1515/rjim-2016-0025.

LUO, Jun-Li *et al.* - Inhibition of NF-kappaB in cancer cells converts inflammation- induced tumor growth mediated by TNFalpha to TRAIL-mediated tumor regression. **Cancer cell**. United States. . ISSN 1535-6108 (Print). 6:3 (2004) 297–305. doi: 10.1016/j.ccr.2004.08.012.

MAEDA, H. *et al.* - Tumor vascular permeability and the EPR effect in macromolecular therapeutics: A review. **Journal of Controlled Release**. . ISSN 01683659. 65:1–2 (2000). doi: 10.1016/S0168-3659(99)00248-5.

MAGHSOUDNIA, Niloufar *et al.* - Mitochondrial delivery of microRNA mimic let-7b to NSCLC cells by PAMAM-based nanoparticles. **Journal of Drug Targeting**. . ISSN 10292330. 28:7–8 (2020). doi: 10.1080/1061186X.2020.1774594.

MAJUMDER, Mousumi *et al.* - COX-2 elevates oncogenic miR-526b in breast cancer by EP4 activation. **Molecular Cancer Research**. . ISSN 15573125. 13:6 (2015). doi: 10.1158/1541-7786.MCR-14-0543.

MAJUMDER, Mousumi *et al.* - COX-2 induces oncogenic micro RNA miR655 in human breast cancer. **Scientific Reports**. . ISSN 20452322. 8:1 (2018). doi: 10.1038/s41598-017-18612-3.

MANTOVANI, Alberto *et al.* - Cancer-related inflammation. **Nature**. . ISSN 00280836. 454:7203 (2008) 436–444. doi: 10.1038/nature07205.

MARQUES, João G. *et al.* - Synthesis and characterization of micelles as carriers of non-steroidal anti-inflammatory drugs (NSAID) for application in breast cancer therapy. **Colloids and Surfaces B: Biointerfaces**. . ISSN 18734367. 113:2014). doi:

10.1016/j.colsurfb.2013.09.037.

MARTINEZ, Jonathan *et al.* - Multistage Nanovectors Enhance the Delivery of Free and Encapsulated Drugs. **Current Drug Targets**. . ISSN 13894501. 16:14 (2015). doi: 10.2174/1389450115666141015113914.

MASOOD, Farha - Polymeric nanoparticles for targeted drug delivery system for cancer therapy. **Materials Science and Engineering C**. . ISSN 18730191. 60:2016). doi: 10.1016/j.msec.2015.11.067.

MATURU, Paramahamsa *et al.* - Role of Cyclooxygenase-2 Pathway in Creating an Immunosuppressive Microenvironment and in Initiation and Progression of Wilms' Tumor. **Neoplasia (United States)**. . ISSN 14765586. 19:3 (2017). doi: 10.1016/j.neo.2016.07.009.

MERRITT, Melissa A. *et al.* - Pre-diagnosis and post-diagnosis use of common analgesics and ovarian cancer prognosis (NHS/NHSII): a cohort study. **The Lancet Oncology**. . ISSN 14745488. 19:8 (2018) 1107–1116. doi: 10.1016/S1470-2045(18)30373-5.

MIAO, Jie *et al.* - Prostaglandin E2 and PD-1 mediated inhibition of antitumor CTL responses in the human tumor microenvironment. **Oncotarget**. . ISSN 19492553. 8:52 (2017). doi: 10.18632/oncotarget.21155.

MOCHALIN, Vadym N. *et al.* - Adsorption of drugs on nanodiamond: Toward development of a drug delivery platform. **Molecular Pharmaceutics**. . ISSN 15438384. 10:10 (2013). doi: 10.1021/mp400213z.

MOLINA, Miguel A. *et al.* - Increased Cyclooxygenase-2 Expression in Human Pancreatic Carcinomas and Cell Lines: Growth Inhibition by Nonsteroidal Anti-Inflammatory Drugs1. **Cancer Research**. . ISSN 0008-5472. 59:17 (1999) 4356–4362.

MOLINARO, Roberto *et al.* - Inflammation and Cancer: In Medio Stat Nano. **Current Medicinal Chemistry**. . ISSN 09298673. 25:34 (2018). doi: 10.2174/0929867324666170920160030.

MORA-HUERTAS, C. E.; FESSI, H.; ELAISSARI, A. - Polymer-based nanocapsules for drug delivery. **International Journal of Pharmaceutics**. . ISSN 0378-5173. 385:1 (2010) 113–142. doi: https://doi.org/10.1016/j.ijpharm.2009.10.018.

MORTEZAEE, Keywan - Human hepatocellular carcinoma: Protection by melatonin. **Journal of Cellular Physiology**. . ISSN 10974652. 233:10 (2018). doi: 10.1002/jcp.26586.

MURATA, Mariko - Inflammation and cancer. **Environmental Health and Preventive**

Medicine. . ISSN 1347-4715. 23:1 (2018) 50. doi: 10.1186/s12199-018-0740-1.

NALDINI, Luigi - Gene therapy returns to centre stage. **Nature**. . ISSN 14764687. 526:7573 (2015). doi: 10.1038/nature15818.

NARAYANAN, Dhanya *et al.* - Poly-(ethylene glycol) modified gelatin nanoparticles for sustained delivery of the anti-inflammatory drug Ibuprofen-Sodium: An in vitro and in vivo analysis. **Nanomedicine: Nanotechnology, Biology and Medicine**. . ISSN 1549-9634. 9:6 (2013) 818–828. doi: https://doi.org/10.1016/j.nano.2013.02.001.

NGUYEN, Don X.; BOS, Paula D.; MASSAGUÉ, Joan - Metastasis: From dissemination to organ-specific colonization. **Nature Reviews Cancer**. . ISSN 1474175X. 9:4 (2009). doi: 10.1038/nrc2622.

NIU, Guilian *et al.* - Signal transducer and activator of transcription 3 is required for hypoxia-inducible factor-1alpha RNA expression in both tumor cells and tumor-associated myeloid cells. **Molecular cancer research : MCR**. . ISSN 1541-7786 (Print). 6:7 (2008) 1099–1105. doi: 10.1158/1541-7786.MCR-07-2177.

OKAMI, Jiro *et al.* - Overexpression of cyclooxygenase-2 in carcinoma of the pancreas. **Clinical Cancer Research**. . ISSN 10780432. 5:8 (1999) 2018–2024. doi: 10.1016/s0016-5085(00)82293-3.

PAL, Tapas; PAUL, Shubhajit; SA, Biswanath - Polymethylmethacrylate Coated Alginate Matrix Microcapsules for Controlled Release of Diclofenac Sodium. **Pharmacology & Pharmacy**. . ISSN 2157-9423. 02:02 (2011). doi: 10.4236/pp.2011.22007.

PAN, Jinshun *et al.* - Cyclooxygenase-2 induced β1-integrin expression in NSCLC and promoted cell invasion via the EP1/MAPK/E2F-1/FoxC2 signal pathway. **Scientific Reports**. . ISSN 20452322. 6:2016). doi: 10.1038/srep33823.

PARRA, Alexander *et al.* - Design and elaboration of freeze-dried PLGA nanoparticles for the transcorneal permeation of carprofen: Ocular anti-inflammatory applications. **Colloids and Surfaces B: Biointerfaces**. . ISSN 0927-7765. 136:2015) 935–943. doi: https://doi.org/10.1016/j.colsurfb.2015.10.026.

PATLOLLA, Ram R. *et al.* - Formulation, characterization and pulmonary deposition of nebulized celecoxib encapsulated nanostructured lipid carriers. **Journal of Controlled Release**. . ISSN 0168-3659. 144:2 (2010) 233–241. doi: https://doi.org/10.1016/j.jconrel.2010.02.006.

PEER, Dan *et al.* - Nanocarriers as an emerging platform for cancer therapy. **Nature**

Nanotechnology. . ISSN 17483387. 2:12 (2007). doi: 10.1038/nnano.2007.387.

PERES, Lauren C. *et al.* - Analgesic medication use and risk of epithelial ovarian cancer in African American women. **British Journal of Cancer**. . ISSN 15321827. 114:7 (2016) 819–825. doi: 10.1038/bjc.2016.39.

PETERSEN, Grant H. *et al.* - Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional non-liposomal doxorubicin. **Journal of Controlled Release**. . ISSN 18734995. 232:2016). doi: 10.1016/j.jconrel.2016.04.028.

PHILLIPS, Margaret A.; GRAN, Martin L.; PEPPAS, Nicholas A. - Targeted nanodelivery of drugs and diagnostics. **Nano Today**. . ISSN 1748-0132. 5:2 (2010) 143–159. doi: https://doi.org/10.1016/j.nantod.2010.03.003.

POKU, Rosemary A. *et al.* - Diclofenac enhances docosahexaenoic acid-induced apoptosis in vitro in lung cancer cells. **Cancers**. . ISSN 20726694. 12:9 (2020) 1–19. doi: 10.3390/cancers12092683.

PRAVEEN, Thaggikuppe Krishnamurthy *et al.* - Inflammation targeted nanomedicines: Patents and applications in cancer therapy. **Seminars in Cancer Biology**. . ISSN 1044-579X. 2022). doi: https://doi.org/10.1016/j.semcancer.2022.04.004.

RAKOFF-NAHOUM, Seth - Why cancer and inflammation? **Yale Journal of Biology and Medicine**. . ISSN 00440086. 79:3–4 (2006).

RAMU, Arunkumar *et al.* - Gramine attenuates EGFR-mediated inflammation and cell proliferation in oral carcinogenesis via regulation of NF-κB and STAT3 signaling. **Biomedicine and Pharmacotherapy**. . ISSN 19506007. 98:2018). doi: 10.1016/j.biopha.2017.12.049.

REFUERZO, Jerrie S. *et al.* - Liposomes: a nanoscale drug carrying system to prevent indomethacin passage to the fetus in a pregnant mouse model. **American Journal of Obstetrics and Gynecology**. . ISSN 0002-9378. 212:4 (2015) 508.e1-508.e7. doi: https://doi.org/10.1016/j.ajog.2015.02.006.

ROBERTS, Heather R. *et al.* - Colon tumour cells increase PGE(2) by regulating COX-2 and 15-PGDH to promote survival during the microenvironmental stress of glucose deprivation. **Carcinogenesis**. England. . ISSN 1460-2180 (Electronic). 32:11 (2011) 1741–1747. doi: 10.1093/carcin/bgr210.

RODRÍGUEZ-MIGUEL, Antonio *et al.* - Population-based case-control study: chemoprotection of colorectal cancer with non-aspirin nonsteroidal anti-inflammatory drugs and other drugs for pain control. **Alimentary Pharmacology and Therapeutics**. . ISSN

13652036. 50:3 (2019) 295–305. doi: 10.1111/apt.15333.

ROSENBLUM, Daniel *et al.* - Progress and challenges towards targeted delivery of cancer therapeutics. **Nature communications**. . ISSN 2041-1723 (Electronic). 9:1 (2018) 1410. doi: 10.1038/s41467-018-03705-y.

ROSENTHAL, Joseph A. *et al.* - Pathogen-like particles: biomimetic vaccine carriers engineered at the nanoscale. **Current opinion in biotechnology**. England. . ISSN 1879-0429 (Electronic). 28:2014) 51–58. doi: 10.1016/j.copbio.2013.11.005.

ROTHWELL, Peter M. *et al.* - Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. **The Lancet**. . ISSN 01406736. 376:9754 (2010). doi: 10.1016/S0140-6736(10)61543-7.

ROY, Bornika; GHOSE, Sampa; BISWAS, Subhrajit - Therapeutic strategies for miRNA delivery to reduce hepatocellular carcinoma. **Seminars in Cell and Developmental Biology**. . ISSN 10963634. 124:2022). doi: 10.1016/j.semcdb.2021.04.006.

RUDER, Elizabeth H. *et al.* - Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. **American Journal of Gastroenterology**. . ISSN 00029270. 106:7 (2011) 1340–1350. doi: 10.1038/ajg.2011.38.

RUGO, Hope S. *et al.* - Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N. **Journal of clinical oncology : official journal of the American Society of Clinical Oncology**. . ISSN 1527-7755 (Electronic). 33:21 (2015) 2361–2369. doi: 10.1200/JCO.2014.59.5298.

RWEI, Alina Y.; WANG, Weiping; KOHANE, Daniel S. - Photoresponsive nanoparticles for drug delivery. **Nano Today**. . ISSN 1748-0132. 10:4 (2015) 451–467. doi: https://doi.org/10.1016/j.nantod.2015.06.004.

SCHAUE, Dörthe *et al.* - Radiation and Inflammation. **Seminars in Radiation Oncology**. . ISSN 15329461. 25:1 (2015). doi: 10.1016/j.semradonc.2014.07.007.

SCHULTHEIS, Beate *et al.* - First-in-human phase I study of the liposomal RNA interference therapeutic Atu027 in patients with advanced solid tumors. **Journal of Clinical Oncology**. . ISSN 15277755. 32:36 (2014). doi: 10.1200/JCO.2013.55.0376.

SENGUPTA, Shiladitya *et al.* - Temporal targeting of tumour cells and neovasculature with a nanoscale delivery system. **Nature**. . ISSN 00280836. 436:7050 (2005). doi:

10.1038/nature03794.

SHACTER, Emily; WEITZMAN, Sigmund A. - Chronic inflammation and cancer. **Oncology (Williston Park, N.Y.)**. . ISSN 08909091. 16:2 (2002).

SHANG, Qing *et al.* - The binary complex of poly(PEGMA-co-MAA) hydrogel and PLGA nanoparticles as a novel oral drug delivery system for ibuprofen delivery. **Journal of Biomaterials Science, Polymer Edition**. 28:16 (2017) 1874–1887. doi: 10.1080/09205063.2017.1354677.

SHARMA, Sherven *et al.* - Tumor cyclooxygenase-2/prostaglandin E2-dependent promotion of FOXP3 expression and CD4+CD25+ T regulatory cell activities in lung cancer. **Cancer Research**. . ISSN 00085472. 65:12 (2005). doi: 10.1158/0008-5472.CAN-05-0141.

SHI, Jinjun *et al.* - Nanotechnology in drug delivery and tissue engineering: From discovery to applications. **Nano Letters**. . ISSN 15306984. 10:9 (2010). doi: 10.1021/nl102184c.

SHI, Jinjun *et al.* - Cancer nanomedicine: progress, challenges and opportunities. **Nature Reviews Cancer**. . ISSN 1474-1768. 17:1 (2017) 20–37. doi: 10.1038/nrc.2016.108.

SHI, Jun *et al.* - Nonsteroidal anti-inflammatory drugs using and risk of head and neck cancer: a dose-response meta analysis of prospective cohort studies. **Oncotarget**. . ISSN 1949-2553 (Electronic). 8:58 (2017) 99066–99074. doi: 10.18632/oncotarget.21524.

SHUKLA, Sourabh *et al.* - To Target or Not to Target: Active vs. Passive Tumor Homing of Filamentous Nanoparticles Based on Potato virus X. **Cellular and molecular bioengineering**. . ISSN 1865-5025 (Print). 8:3 (2015) 433–444. doi: 10.1007/s12195-015-0388-5.

SILVEIRA, Elita F. DA *et al.* - Ketoprofen-loaded polymeric nanocapsules selectively inhibit cancer cell growth in vitro and in preclinical model of glioblastoma multiforme. **Investigational New Drugs**. . ISSN 01676997. 31:6 (2013). doi: 10.1007/s10637-013-0016-y.

SINGH, Balraj *et al.* - COX-2 induces IL-11 production in human breast cancer cells. Em **Journal of Surgical Research**

SMITH, Andrew - Big moment for nanotech: oncology therapeutics poised for a leap. **OncologyLive**. 2013).

SMITH, Douglas M.; SIMON, Jakub K.; BAKER, James R. Jr - Applications of nanotechnology for immunology. **Nature reviews. Immunology**. . ISSN 1474-1741 (Electronic). 13:8 (2013)

592–605. doi: 10.1038/nri3488.

SONG, Shiping *et al.* - Functional nanoprobes for ultrasensitive detection of biomolecules. **Chemical Society reviews**. England. . ISSN 1460-4744 (Electronic). 39:11 (2010) 4234–4243. doi: 10.1039/c000682n.

SOSLOW, Robert A. *et al.* - COX-2 is expressed in human pulmonary, colonic, and mammary tumors. **Cancer**. . ISSN 0008543X. 89:12 (2000) 2637–2645. doi: 10.1002/1097-0142(20001215)89:12<2637::AID-CNCR17>3.0.CO;2-B.

SOSTRES, Carlos *et al.* - Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. **Best Practice and Research: Clinical Gastroenterology**. . ISSN 15216918. 24:2 (2010). doi: 10.1016/j.bpg.2009.11.005.

SRINATH, P. *et al.* - Long-circulating liposomes of indomethacin in arthritic rats — a biodisposition study. **Pharmaceutica Acta Helvetiae**. . ISSN 0031-6865. 74:4 (2000) 399–404. doi: https://doi.org/10.1016/S0031-6865(00)00023-6.

STATHOPOULOS, G. P. *et al.* - Liposomal cisplatin combined with paclitaxel versus cisplatin and paclitaxel in non-small-cell lung cancer: A randomized phase III multicenter trial. **Annals of Oncology**. . ISSN 09237534. 21:11 (2010). doi: 10.1093/annonc/mdq234.

SULLIVAN, N. J. *et al.* - Interleukin-6 induces an epithelial-mesenchymal transition phenotype in human breast cancer cells. **Oncogene**. . ISSN 09509232. 28:33 (2009). doi: 10.1038/onc.2009.180.

SUNG, Hyuna *et al.* - Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. **CA: A Cancer Journal for Clinicians**. . ISSN 0007-9235. 71:3 (2021). doi: 10.3322/caac.21660.

SVENSON, Sonke - Clinical translation of nanomedicines. **Current Opinion in Solid State and Materials Science**. . ISSN 13590286. 16:6 (2012). doi: 10.1016/j.cossms.2012.10.001.

SWARTZ, Melody A.; HIROSUE, Sachiko; HUBBELL, Jeffrey A. - Engineering approaches to immunotherapy. **Science Translational Medicine**. . ISSN 19466234. 4:148 (2012). doi: 10.1126/scitranslmed.3003763.

TABERNERO, Josep *et al.* - First-in-humans trial of an RNA interference therapeutic targeting VEGF and KSP in cancer patients with liver involvement. **Cancer Discovery**. . ISSN 21598274. 3:4 (2013). doi: 10.1158/2159-8290.CD-12-0429.

TANG, Weiwei *et al.* - The mechanisms of sorafenib resistance in hepatocellular carcinoma:

theoretical basis and therapeutic aspects. **Signal Transduction and Targeted Therapy**. . ISSN 20593635. 5:1 (2020). doi: 10.1038/s41392-020-0187-x.

TANIGUCHI, Koji; KARIN, Michael - NF-κB, inflammation, immunity and cancer: coming of age. **Nature Reviews Immunology**. . ISSN 1474-1741. 18:5 (2018) 309–324. doi: 10.1038/nri.2017.142.

TARACH, Piotr; JANASZEWSKA, Anna - Recent advances in preclinical research using pamam dendrimers for cancer gene therapy. **International Journal of Molecular Sciences**. . ISSN 14220067. 22:6 (2021). doi: 10.3390/ijms22062912.

TESNIERE, A. *et al.* - Molecular characteristics of immunogenic cancer cell death. **Cell Death and Differentiation**. . ISSN 13509047. 15:1 (2008). doi: 10.1038/sj.cdd.4402269.

THAKKAR, Arvind *et al.* - Ferulic acid combined with aspirin demonstrates chemopreventive potential towards pancreatic cancer when delivered using chitosan-coated solid-lipid nanoparticles. **Cell and Bioscience**. . ISSN 20453701. 5:1 (2015). doi: 10.1186/s13578-015-0041-y.

THUN, Michael J.; JANE HENLEY, S.; PATRONO, Carlo - Nonsteroidal anti-inflammatory drugs as anticancer agents: Mechanistic, pharmacologic, and clinical issues. **Journal of the National Cancer Institute**. . ISSN 00278874. 94:4 (2002). doi: 10.1093/jnci/94.4.252.

TODORIC, Jelena; ANTONUCCI, Laura; KARIN, Michael - Targeting inflammation in cancer prevention and therapy. **Cancer Prevention Research**. . ISSN 19406215. 9:12 (2016). doi: 10.1158/1940-6207.CAPR-16-0209.

TOLCHER, Anthony W. *et al.* - A phase 1 study of the BCL2-targeted deoxyribonucleic acid inhibitor (DNAi) PNT2258 in patients with advanced solid tumors. **Cancer Chemotherapy and Pharmacology**. . ISSN 14320843. 73:2 (2014). doi: 10.1007/s00280-013-2361-0.

TONG, Dali *et al.* - Metformin inhibits castration-induced EMT in prostate cancer by repressing COX2/PGE2/STAT3 axis. **Cancer Letters**. . ISSN 18727980. 389:2017). doi: 10.1016/j.canlet.2016.12.031.

TRABERT, Britton *et al.* - Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: A pooled analysis in the ovarian cancer association consortium. **Journal of the National Cancer Institute**. . ISSN 14602105. 106:2 (2014). doi: 10.1093/jnci/djt431.

TRABERT, Britton *et al.* - Analgesic use and ovarian cancer risk: An analysis in the Ovarian Cancer Cohort Consortium. **Journal of the National Cancer Institute**. . ISSN 14602105.

111:2 (2019) 137–145. doi: 10.1093/jnci/djy100.

TRÉDAN, Olivier *et al.* - Drug resistance and the solid tumor microenvironment. **Journal of the National Cancer Institute**. . ISSN 00278874. 99:19 (2007). doi: 10.1093/jnci/djm135.

ULRICH, Cornelia M.; BIGLER, Jeannette; POTTER, John D. - Non-steroidal anti-inflammatory drugs for cancer prevention: Promise, perils and pharmacogenetics. **Nature Reviews Cancer**. . ISSN 1474175X. 6:2 (2006). doi: 10.1038/nrc1801.

US NATIONAL LIBRARY OF MEDICINE - **A Phase III Study of NK105 in Patients With Breast Cancer.** 2014. Disponível em: https://clinicaltrials.gov/ct2/show/NCT00964080?term

US NATIONAL LIBRARY OF MEDICINE - **Anti-EGFR Immunoliposomes in Solid Tumors**, 2014. [Consult. 15 jun. 2022] Disponível: https://clinicaltrials.gov/ct2/show/NCT01702129

US NATIONAL LIBRARY OF MEDICINE - **Safety and Tolerability Study of SNS01-T in Relapsed or Refractory B Cell Malignancies (Multiple Myeloma, B Cell Lymphoma, or Plasma Cell Leukemia (PCL)**. 2014. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT01435720?term

US NATIONAL LIBRARY OF MEDICINE - **Study of MBP-426 in Patients With Second Line Gastric, Gastroesophageal, or Esophageal Adenocarcinoma**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT01644890?term

US NATIONAL LIBRARY OF MEDICINE - **MM-302 Plus Trastuzumab vs. Chemotherapy of Physician's Choice Plus Trastuzumab in HER2-Positive Locally Advanced/Metastatic Breast Cancer Patients (HERMIONE)**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT02213744?term

US NATIONAL LIBRARY OF MEDICINE - **Study of ThermoDox With Standardized Radiofrequency Ablation (RFA) for Treatment of Hepatocellular Carcinoma (HCC) (OPTIMA)**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT02112656?term

US NATIONAL LIBRARY OF MEDICINE - **Phase III Study of CPX-351 Versus 7+3 in Patients 60-75 Years Old With Untreated High Risk (Secondary) Acute Myeloid Leukemia (301)**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT01696084?term

US NATIONAL LIBRARY OF MEDICINE - **Multicenter Study Of CPX-1 (Irinotecan HCl: Floxuridine) Liposome Injection In Patients With Advanced Colorectal**

Cancer. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT00361842?term

US NATIONAL LIBRARY OF MEDICINE - **Pilot Study of AuroLase(tm) Therapy in Refractory and/or Recurrent Tumors of the Head and Neck**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT00848042?term

US NATIONAL LIBRARY OF MEDICINE - **NBTXR3 Crystalline Nanoparticles and Radiation Therapy in Treating Randomized Patients in Two Arms With Soft Tissue Sarcoma of the Extremity and Trunk Wall**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT02379845?term

US NATIONAL LIBRARY OF MEDICINE - **Phase II Study of Combined Temozolomide and SGT-53 for Treatment of Recurrent Glioblastoma**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT02340156?term

US NATIONAL LIBRARY OF MEDICINE - **Study of Combined SGT-53 Plus Gemcitabine/Nab-Paclitaxel for Metastatic Pancreatic Cancer**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT02340117?term

US NATIONAL LIBRARY OF MEDICINE - **Atu027 Plus Gemcitabine in Advanced or Metastatic Pancreatic Cancer (Atu027-I-02) (Atu027-I-02)**. 2016. [Consult. 15 jun. 2022]. Disponível em: https://clinicaltrials.gov/ct2/show/NCT01808638?term

VANE, J. R.; BOTTING, R. M. - Mechanism of action of nonsteroidal anti-inflammatory drugs. **The American journal of medicine**. United States. . ISSN 0002-9343 (Print). 104:3A (1998) 2S-8S; discussion 21S-22S. doi: 10.1016/s0002-9343(97)00203-9.

VASAN, Neil; BASELGA, José; HYMAN, David M. - A view on drug resistance in cancer. **Nature**. . ISSN 14764687. 575:7782 (2019). doi: 10.1038/s41586-019-1730-1.

VENKATESAN, P. *et al.* - The potential of celecoxib-loaded hydroxyapatite-chitosan nanocomposite for the treatment of colon cancer. **Biomaterials**. . ISSN 01429612. 32:15 (2011). doi: 10.1016/j.biomaterials.2011.01.027.

VIDAL, Adriana C. *et al.* - Aspirin, NSAIDs, and risk of prostate cancer: Results from the REDUCE study. **Clinical Cancer Research**. . ISSN 15573265. 21:4 (2015) 756–762. doi: 10.1158/1078-0432.CCR-14-2235.

VOGT, T. *et al.* - Progression and NSAID-induced apoptosis in malignant melanomas are independent of cyclooxygenase II. **Melanoma research**. England. . ISSN 0960-8931 (Print). 11:6 (2001) 587–599. doi: 10.1097/00008390-200112000-00005.

VORONOV, Elena *et al.* - IL-1 is required for tumor invasiveness and angiogenesis. **Proceedings of the National Academy of Sciences of the United States of America**. . ISSN 00278424. 100:5 (2003). doi: 10.1073/pnas.0437939100.

WANG, Andrew Z.; LANGER, Robert; FAROKHZAD, Omid C. - Nanoparticle delivery of cancer drugs. **Annual Review of Medicine**. . ISSN 00664219. 63:2012) 185–198. doi: 10.1146/annurev-med-040210-162544.

WEI, Yumeng *et al.* - Paclitaxel targeting to lungs by way of liposomes prepared by the effervescent dispersion technique. **Archives of Pharmacal Research**. . ISSN 19763786. 37:6 (2014). doi: 10.1007/s12272-013-0181-8.

WOLFRAM, Joy; FERRARI, Mauro - Clinical cancer nanomedicine. **Nano Today**. . ISSN 1878044X. 25:2019) 85–98. doi: 10.1016/j.nantod.2019.02.005.

WONG, Rebecca S. Y. - Role of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Cancer Prevention and Cancer Promotion. **Advances in Pharmacological Sciences**. . ISSN 16876342. 2019:2019). doi: 10.1155/2019/3418975.

WONGRAKPANICH, Supakanya *et al.* - A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. **Aging and Disease**. . ISSN 21525250. 9:1 (2018). doi: 10.14336/AD.2017.0306.

WU, Yadi *et al.* - Stabilization of snail by NF-kappaB is required for inflammation-induced cell migration and invasion. **Cancer cell**. . ISSN 1878-3686 (Electronic). 15:5 (2009) 416–428. doi: 10.1016/j.ccr.2009.03.016.

XIANG, Shuanglin *et al.* - Aspirin inhibits ErbB2 to induce apoptosis in cervical cancer cells. **Medical Oncology**. . ISSN 13570560. 27:2 (2010). doi: 10.1007/s12032-009-9221-0.

XU, Lihong *et al.* - COX-2 Inhibition Potentiates Anti-Angiogenic Cancer Therapy and Prevents Metastasis in Preclinical Models HHS Public Access One Sentence Summary: COX-2 Blockade Potentiates Anti-Angiogenic Therapy. **Sci Transl Med**. 6:242 (2014) 242–84. doi: 10.1126/scitranslmed.3008455.COX-2.

YANG, Jing; WEINBERG, Robert A. - Epithelial-Mesenchymal Transition: At the Crossroads of Development and Tumor Metastasis. **Developmental Cell**. . ISSN 15345807. 14:6 (2008). doi: 10.1016/j.devcel.2008.05.009.

YAO, Min *et al.* - Effects of nonselective cyclooxygenase inhibition with low-dose ibuprofen on tumor growth, angiogenesis, metastasis, and survival in a mouse model of colorectal cancer. **Clinical Cancer Research**. . ISSN 10780432. 11:4 (2005). doi: 10.1158/1078-0432.CCR-04-

1696.

YILDIZ, Ibrahim; SHUKLA, Sourabh; STEINMETZ, Nicole F. - Applications of viral nanoparticles in medicine. **Current Opinion in Biotechnology**. . ISSN 09581669. 22:6 (2011). doi: 10.1016/j.copbio.2011.04.020.

YLÄ-HERTTUALA, Seppo - Endgame: Glybera finally recommended for approval as the first gene therapy drug in the European union. **Molecular Therapy**. . ISSN 15250016. 20:10 (2012). doi: 10.1038/mt.2012.194.

YU, Hua; KORTYLEWSKI, Marcin; PARDOLL, Drew - Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. **Nature reviews. Immunology**. England. . ISSN 1474-1733 (Print). 7:1 (2007) 41–51. doi: 10.1038/nri1995.

ZHANG, Kailiang *et al.* - Extracellular vesicle-mediated delivery of miR-101 inhibits lung metastasis in osteosarcoma. **Theranostics**. . ISSN 18387640. 10:1 (2020). doi: 10.7150/thno.33482.

ZHANG, Xuemei *et al.* - Methotrexate-loaded PLGA nanobubbles for ultrasound imaging and Synergistic Targeted therapy of residual tumor during HIFU ablation. **Biomaterials**. . ISSN 18785905. 35:19 (2014). doi: 10.1016/j.biomaterials.2014.02.036.

ZHANG, Yan Peng *et al.* - Aspirin might reduce the incidence of pancreatic cancer: A meta-analysis of observational studies. **Scientific Reports**. . ISSN 20452322. 5:2015) 1–12. doi: 10.1038/srep15460.

ZHAO, Huakan *et al.* - Inflammation and tumor progression: signaling pathways and targeted intervention. **Signal Transduction and Targeted Therapy**. . ISSN 2059-3635. 6:1 (2021) 263. doi: 10.1038/s41392-021-00658-5.