A combination of carrier erythrocytes and artificial nanoparticles as a promising approach for drug delivery

N.K. Athukorala
S/15/009
Department of Molecular Biology & Biotechnology

NEWS | IN DEPTH

BIOMEDICINE

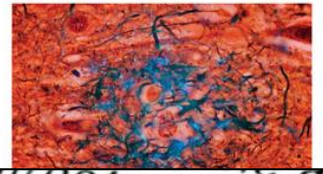
Doubts persist for claimed Alzheimer's drug

Once declared a failure, Biogen's antibody drug to be submitted for U.S. approval in 2020

By Kelly Servick

Last week, with trading in the company's stock halted for the widely anticipated event, Biogen gave its first scientific presentation in defense of its startling claim to have developed the first drug that can change the devastating course of Alzheimer's disease. But some scientists and analysts had hoped for more detail, and the community remains divided over whether the drug is a turning point in the quest for an Alzheimer's treatment—or a false hope.

At the Clinical Trials on Alzheimer's Disease congress in San Diego, California, Samantha Budd Haeberlein, Biogen's head of clinical development, tried to clarify what had emboldened the Cambridge, Massachusetts–based biotech to say in October it would soon ask the U.S. Food and Drug Administration (FDA) to approve its drug, aducanumab. That announcement was a striking turnaround for a drug the company had publicly abandoned in March after a discouraging preliminary analysis. But after examining more patient data, she explained, investigators found in one trial



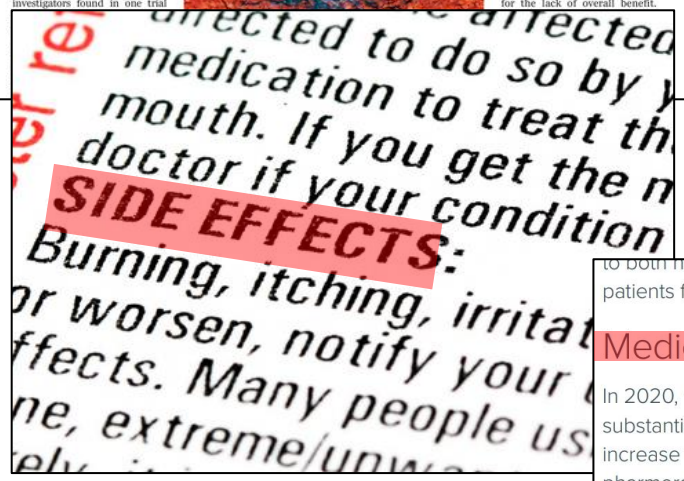
ties that suggest aducanumab helped trial participants retain some independence. "Those of us who know this disease well know what it means to lose yourself, slice by slice, and anything you can hang on to and do well is a triumph."

Aducanumab is among the last potential drugs standing that targets beta amyloid, the protein fragment that forms sticky plaques around neurons in the brains of people with Alzheimer's. The failure of several antiamyloid drugs in large clinical trials have suggested that plaque buildup, though a hallmark of Alzheimer's, might be the wrong target for stopping disease progression once people show symptoms.

the high-dose group showed less cognitive decline than the placebo group, based on a standard dementia rating scale. But in ENGAGE, the high-dose group declined slightly more than the placebo group.

Budd Haeberlein tried last week to explain the conflicting results. A major factor, she said, was how the trials treated participants who had a genetic variant called *APOE4*. Those participants had an increased risk of brain swelling—a side effect of antiamyloid antibodies that occurred in about one-third of people getting the high dose and can cause symptoms such as headache, dizziness, and nausea. Patients in both arms with *APOE4* received a reduced amount of the antibody at first, as a precaution, but in 2017, the researchers decided they could safely ramp up.

ENGAGE started about 1 month before EMERGE and had more participants already enrolled at the time of the change. As a result, a smaller proportion of its participants got a full, uninterrupted course of the maximum dose—15% versus 21% in EMERGE, which might account for the lack of overall benefit.



to both higher prices per unit and the mix of newer medicines that bring meaningful clinical benefit to patients facing a wide range of diseases.

Medicine use in 2020

In 2020, more of the world's population will have access to medicine than ever before, albeit with substantial disparities. Patients will receive 4.5 trillion doses, up 24% from 2015, with most of the increase from countries closing the gap in per capita usage of medicines between developed and pharmerging countries. Over 50% of the world's population will consume more than 1 dose per

CELEBRATING 40 YEARS OF EXCELLENCE IN PUBLISHING

October 5, 2018 • Volume 40, Number 19

oncology-times.com

ONCOLOGY TIMES®

Independent News on HEMATOLOGY / ONCOLOGY

New Treatments for Relapsed Hematologic Malignancies After alloHCT

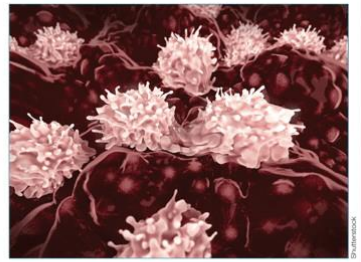
BY JACQUELINE S. GARCIA, MD, & MATTHEW S. DAVIDS, MD, MMSc

Relapse remains the leading cause of treatment failure for patients with hematologic malignancies who undergo allogeneic hematopoietic cell transplantation (alloHCT). For example, patients with acute myeloid leukemia (AML) who relapse shortly after transplant have a particularly poor outcome, with a 3-year overall survival rate of <5 percent (*Biol Blood Marrow Transplant* 2015;454-459). Such patients commonly receive intensive chemotherapy, but outcomes with this approach are often poor. Therefore, therapeutic strategies to augment a graft-versus-tumor (GVT) effect without eliciting graft-versus-host disease (GVHD) have been explored.

CME Article

However, these strategies, such as withdrawal of immunosuppression, donor lymphocyte

Continued on page 2



Shutterstock

Pioneer Takes Aim at Solid Tumors With T Cells

BY VALERIE NEFF NEWITT

Great men and women of medi- one of history's darkest periods guided his Bethesda, Md., office. "I was born in impression- him toward a monumental career envel- 1940. When I was 5 or 6 years old, virtu- individual oping medical "firsts" that continue to ally all of my parents' families were wiped mapped shape the emerging potential of adoptive out in the Holocaust. I remember seeing ectional in- cell therapies (ACT) and the aggregate postcards arriving in the mail saying this cation, and field of oncology. relative died at Auschwitz, and that rela- , MD, PhD, "My parents were born in Poland tive died at Buchenwald. It was a horrible at the NCI, and came here to escape persecution," experience. I learned that people could said Rosenberg speaking by phone from be evil; I wanted to be the opposite. Oh sure, I originally wanted to be a cowboy. But by 6 years of age, I converted to medicine."

That conversion eventually resulted in Rosenberg earning a PhD in biophysics, graduating from medical school, and embracing an early belief in the power

Solving a Central Mystery of a Baffling High-Risk Leukemia

St. Jude Children's Research Hospital investigators have unraveled the origins and identified mutations associated with a perplexing form of acute leukemia. The landmark study lays the foundation for more effective treatment of patients with the high-risk cancer (*Nature* 2018; https://doi.org/10.1038/s41586-018-0436-0).

The research focused on mixed phenotype acute leukemia (MPAL), a subtype of acute leukemia that accounts for about 3 percent of the estimated 3,500 pediatric cases of acute leukemia diagnosed annually in the U.S. MPAL also occurs in adults. Their treatment is complicated because MPAL does not fit cleanly into a single diagnosis, but it includes features of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). These markers, which help determine treatment, sometimes change with time or treatment, in some cases enough to change the diagnosis from MPAL to AML or vice versa.

"ALL and AML have very different treatments. But MPAL has features of both, so the question of how best to treat patients with MPAL has been challenging the leukemia community worldwide—and long-term survival of patients has been poor," said Charles Mullighan, MBBS, MD, a member of the St. Jude Department of Pathology. He and Hiroto Inaba, MD, PhD, an associate member of the St. Jude Department of Oncology, are the study's corresponding authors. Long-term survival for young MPAL patients is 47-75 percent, compared to more than 90 percent for young ALL patients and 65-75 percent for AML.

Does FDA approval assures the safety of a medicine?

Research

JAMA | Original Investigation

Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD; Nilay D. Shah, PhD; Jenerius A. Aminawung, MD, MPH; Alison M. Pease, BS; Jean-David Zeitoun, MD, MHPM; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

Supplemental content

IMPORTANCE Postmarket safety events of novel pharmaceuticals and biologics occur when new safety risks are identified after initial regulatory approval of these therapeutics. These safety events can change how novel therapeutics are used in clinical practice and inform patient and clinician decision making.

OBJECTIVES To characterize the frequency of postmarket safety events among novel

Overall failure rate in drug development is extremely high (Hingorani et al., 2019)

This presentation aims to

- ✓ Discuss the importance of drug delivery
- ✓ What made a combined drug delivery strategy to emerge?
- ✓ Significance of a combined drug delivery strategy

Contents

- ✓ Drug delivery and importance
- ✓ Impact from nanotechnology
- ✓ Drawbacks in nanotechnology
- ✓ Cell-based drug delivery platforms
- ✓ Nanoparticles camouflaged with erythrocyte membrane

Drug delivery and it’s importance

- ✓ A research field investigating the methods of administrating a pharmaceutical compound to achieve a therapeutic response (Tiwari et al., 2012)

- ✓ Evolved to address the challenges associated with conventional drug administration

Figure 1: Testing a new drug delivery technology.

- ✓ The vehicles used to deliver the therapeutic compounds to the specific site are known as nanocarriers.

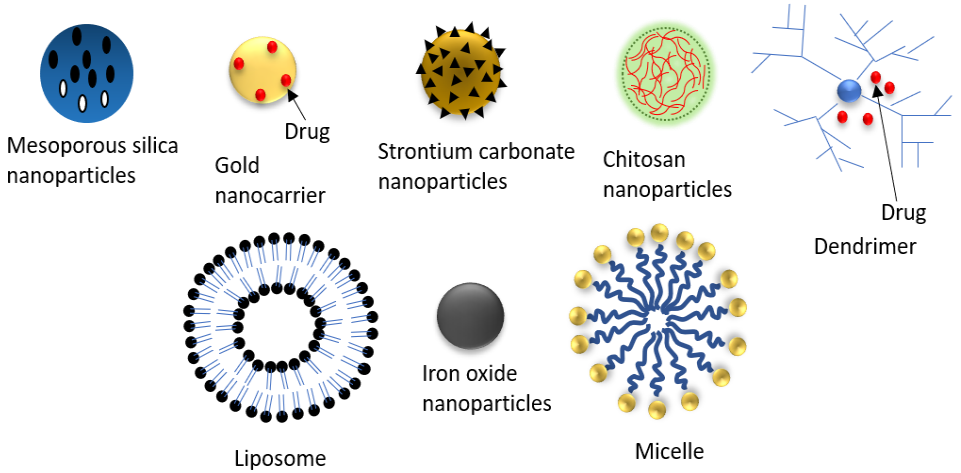


Figure 2: Nanocarriers that can be used to carry drugs.

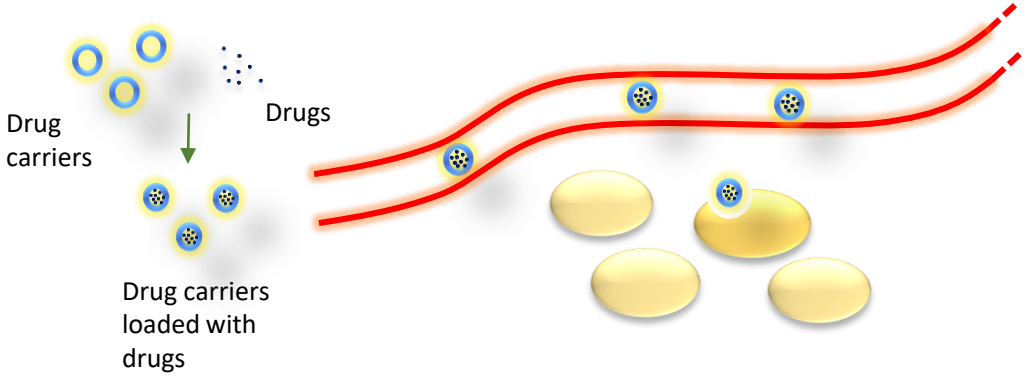


Figure 3: Drug carriers delivering the drug to the desired site.

Impact from Nanotechnology

What is Nanotechnology?

- ✓ The science and engineering of matter at a nanoscale
  (The National Nanotechnology Initiative)

What is Nanomedicine?

- ✓ One offshoot of nanotechnology
- ✓ Applies the knowledge of nanotechnology to treat and prevent diseases

Targeted drug delivery

✓ Active targeting: Using ligand-conjugated nanocarriers

- Therapeutic efficacy
- Increases their cellular uptake
- Less or no damage on normal healthy cells (Namgung et al., 2014)

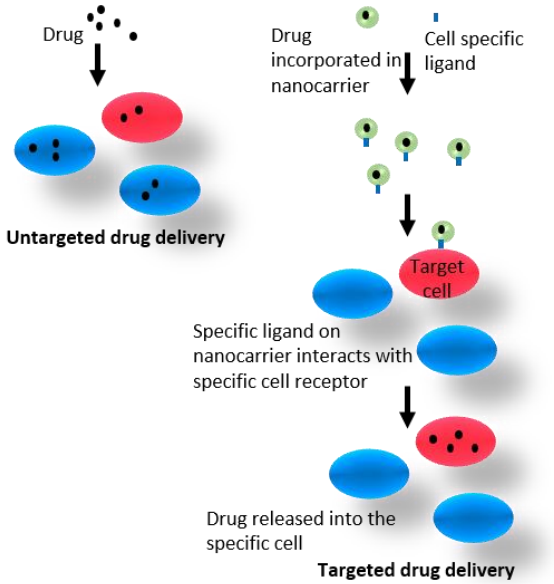


Figure 4: Targeted drug delivery

Co-delivery of drugs

- ✓ Delivery of dual drugs or a drug and a gene
- ✓ Used in cancer chemotherapy
- ✓ Shows high anti-cancer impact
- ✓ Co-delivery of traditional medicines show low toxicity (Guo et al., 2020)

Nanotechnology's role in the race to discover a COVID-19 vaccine

- Safer m-RNA based vaccines to battle COVID-19
- m-RNA needs a carrier for safe delivery

The vehicle of choice are lipid nanoparticles **(**Nanomedicine and the COVID-19 vaccines. Nature Nanotechnology**)**

Figure 4: COVID-19 vaccines. Source: https://qz.com/1931483/is-the-pfizer-vaccine-a-live-virus/

Nanomedicine a false promise?

Potential benefits

- Potential to revolutionize individual and population based health (Pautler and Brenner, 2010)

Possible challenges

- Toxicity (Hussain et al., 2005)
- Pseudoallergy
- Rapid clearance (Guan et al., 2018)

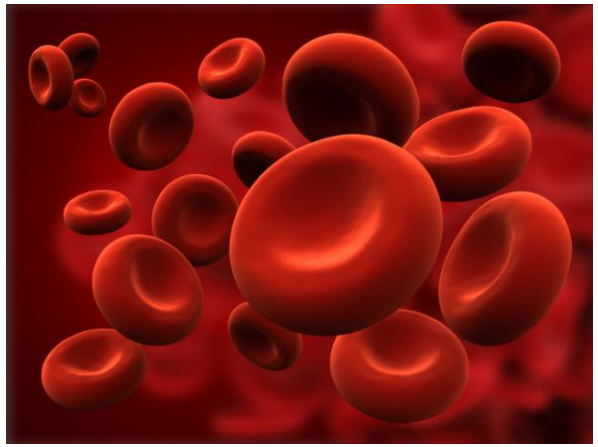
Translation of nanomedicine from bench to bedside

Cell-based drug delivery platforms

- ✓ Evolved as an alternative to micro- and nano-particles
- ✓ Cells used to modify nanoparticles: Erythrocytes (Rossi et al., 2001), platelets (Xu et al., 2017), leukocytes (Palomba et al., 2016), etc.
- ✓ Can combine with nanoparticles to minimize the challenges associated with nanomedicine

Erythrocytes as potential carriers

- ✓ Biocompatible and biodegradable
- ✓ Capable of targeted drug delivery (Talwar and Jain, 1992)
- ✓ CD47 acts as a marker of self (Oldenborg et al., 2000)
- ✓ Biconcave shape optimize flow properties
- ✓ Efficient isolation and preparation of RBC vesicles



Amalgamating natural erythrocytes and synthetic nanocarriers

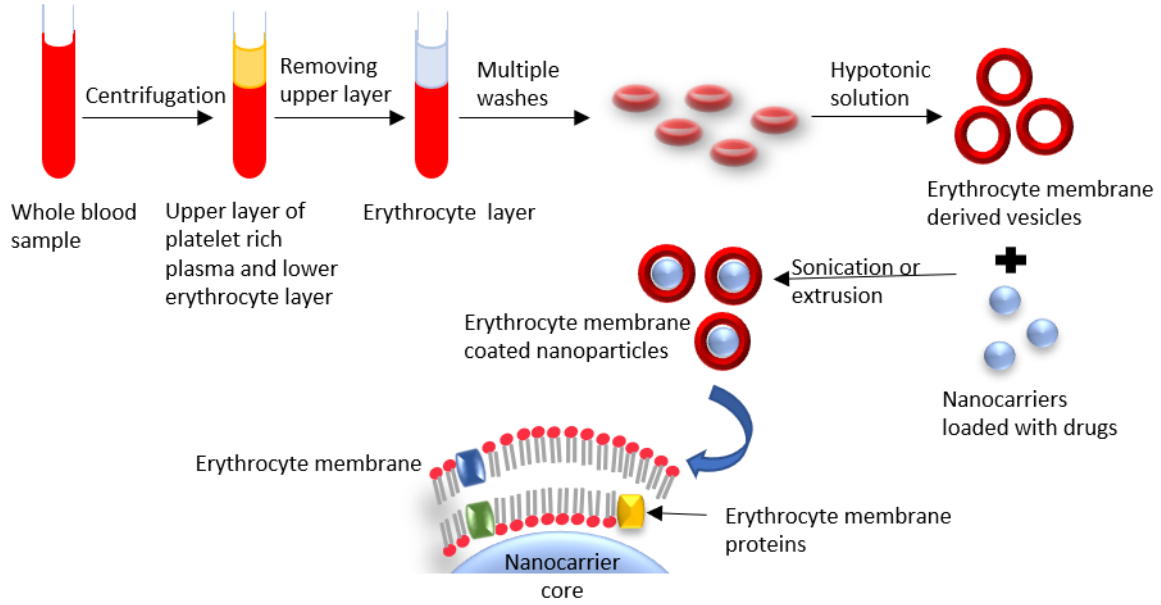
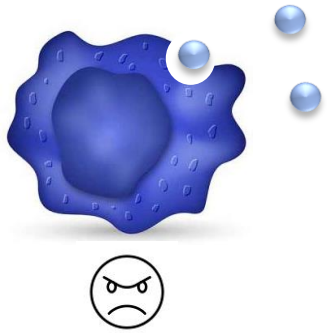
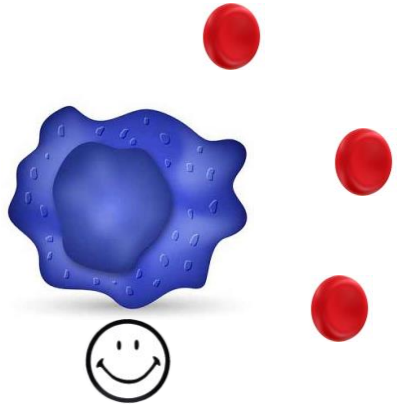


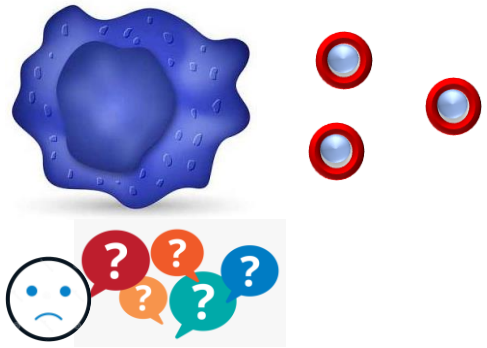
Figure 5: Preparation of RBC membrane coated nanocarriers loaded with drugs



Macrophages phagocytose foreign nanoparticles



Macrophages do not phagocytose erythrocytes



Nanoparticles camouflaged with erythrocyte membrane, mislead macrophages

Figure 6: Coated nanoparticles achieving enhanced retention.

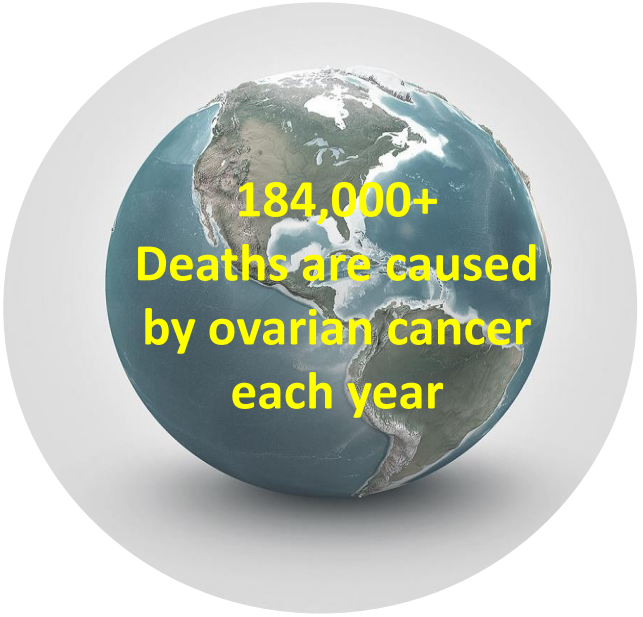
Nanoparticles camouflaged with erythrocyte membrane as a promising approach

Neutralize nanomedicines' limitations

- Biocompatible
- Enhanced retention (Su et al., 2017)
- Efficient drug release
- Overcome cytotoxicity (Ak and Sanlier, 2020)

Broaden nanotechnology's applications and significance

- Allows targeted delivery
  To treat ovarian cancer: Folate receptor-interacting doxorubicin-loaded magnetic nanoparticles camouflaged with erythrocyte membrane vesicles (Ak and Sanlier, 2020).



Statistics available at:
https://berwickpharmacy.com.au/world-ovarian-cancer-day/

- Phototherapy

  Membrane coated gold nanocages in photothermal cancer therapy (Piao et al., 2014)

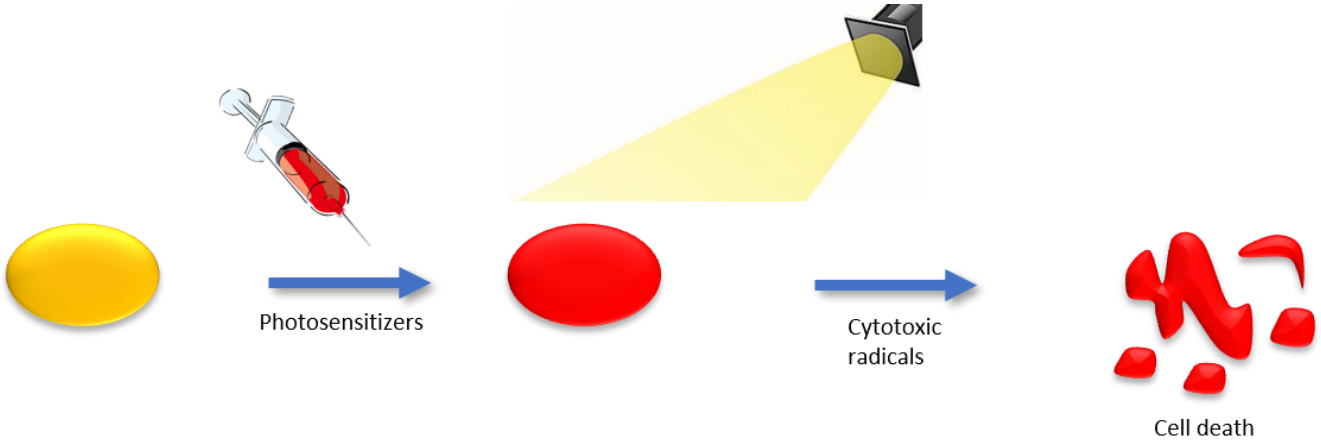


Figure 7: Phototherapy to kill cancer cells

- Significance in toxin vaccination

  Safe delivery of pore-forming toxin for immune processing (Hu et al., 2013)

A camouflage comprised of natural erythrocyte membrane vesicles and synthetic nanoparticles loaded with drugs

- ✓ Combines the advantages of the two partners
- ✓ Neutralizes the disadvantages of the two partners
- ✓ Provides relief to severe diseases

References

1. Hingorani, A.D., Kuan, V., Finan, C., Kruger, F.A., Gaulton, A., Chopade, S. *et al*, S., 2019. Improving the odds of drug development success through human genomics: modelling study. *Scientific reports*, *9*(1), pp.1-25.
2. Tiwari, G., Tiwari, R., Sriwastawa, B., Bhati, L., Pandey, S., Pandey, P. *et al*, S.K., 2012. Drug delivery systems: An updated review. *International journal of pharmaceutical investigation*, *2*(1), p.2.
3. Roco, M.C., 2007. National nanotechnology initiative-past, present, future. *Handbook on nanoscience, engineering and technology*, *2*.
4. Namgung, R., Lee, Y.M., Kim, J., Jang, Y., Lee, B.H., Kim, I.S. *et al*, W.J., 2014. Poly-cyclodextrin and poly-paclitaxel nano-assembly for anticancer therapy. *Nature communications*, *5*(1), pp.1-12.
5. Costin, G.E., Trif, M., Nichita, N., Dwek, R.A. and Petrescu, S.M., 2002. pH-sensitive liposomes are efficient carriers for endoplasmic reticulum-targeted drugs in mouse melanoma cells. *Biochemical and biophysical research communications*, *293*(3), pp.918-923.
6. Guo, W., Song, Y., Song, W., Liu, Y., Liu, Z., Zhang, D. *et al*, O., 2020. co-delivery of Doxorubicin and curcumin with polypeptide nanocarrier for Synergistic Lymphoma therapy. *Scientific Reports*, *10*(1), pp.1-16.
7. Nanomedicine and the COVID-19 vaccines. Nature Nanotechnology. 15, 963 (2020). https://doi.org/10.1038/s41565-020-00820-0.
8. Foley, KE. 2020, Pfizer’s vaccine candidate would be the first of its kind, Quartz, viewed 25 December 2020, <https://qz.com/1931483/is-the-pfizer-vaccine-a-live-virus/>.
9. Pautler, M. and Brenner, S., 2010. Nanomedicine: promises and challenges for the future of public health. *International journal of nanomedicine*, *5*, p.803.
10. Hussain, S.M., Hess, K.L., Gearhart, J.M., Geiss, K.T. and Schlager, J.J., 2005. In vitro toxicity of nanoparticles in BRL 3A rat liver cells. *Toxicology in vitro*, *19*(7), pp.975-983.
11. Guan, J., Shen, Q., Zhang, Z., Jiang, Z., Yang, Y., Lou, M. *et al*, 2018. Enhanced immune compatibility of ligand-targeted liposomes by attenuating natural IgM absorption. *Nature communications*, *9*(1), pp.1-11.

12. Rossi, L., Serafini, S., Cenerini, L., Picardi, F., Bigi, L., Panzani, I. *et al*, 2001. Erythrocyte-mediated delivery of dexamethasone in patients with chronic obstructive pulmonary disease. *Biotechnology and applied biochemistry*, *33*(2), pp.85-89.
13. Xu, P., Zuo, H., Chen, B., Wang, R., Ahmed, A., Hu, Y. *et al*, 2017. Doxorubicin-loaded platelets as a smart drug delivery system: An improved therapy for lymphoma. *Scientific reports*, *7*, p.42632.
14. Palomba, R., Parodi, A., Evangelopoulos, M., Acciardo, S., Corbo, C., De Rosa, E. *et al*, J., 2016. Biomimetic carriers mimicking leukocyte plasma membrane to increase tumor vasculature permeability. *Scientific reports*, *6*(1), pp.1-11.
15. Talwar, N. and Jain, N.K., 1992. Erythrocytes as carriers of primaquine-preparation: characterization and evaluation. *Journal of controlled release*, *20*(2), pp.133-141.
16. Oldenborg, P.A., Zheleznyak, A., Fang, Y.F., Lagenaur, C.F., Gresham, H.D. and Lindberg, F.P., 2000. Role of CD47 as a marker of self on red blood cells. *Science*, *288*(5473), pp.2051-2054.
17. Su, J., Sun, H., Meng, Q., Zhang, P., Yin, Q. and Li, Y., 2017. Enhanced blood suspensibility and laser-activated tumor-specific drug release of theranostic mesoporous silica nanoparticles by functionalizing with erythrocyte membranes. *Theranostics*, *7*(3), p.523.
18. Ak, G. and Şanlıer, Ş.H., 2020. Erythrocyte membrane vesicles coated biomimetic and targeted doxorubicin nanocarrier: Development, characterization and in vitro studies. *Journal of Molecular Structure*, *1205*, p.127664.
19. Berwick Pharmacy, World ovarian cancer day, viewed 25 December 2020, https://berwickpharmacy.com.au/world-ovarian-cancer-day/.
20. Piao, J.G., Wang, L., Gao, F., You, Y.Z., Xiong, Y. and Yang, L., 2014. Erythrocyte membrane is an alternative coating to polyethylene glycol for prolonging the circulation lifetime of gold nanocages for photothermal therapy. *ACS nano*, *8*(10), pp.10414-10425.
21. Hu, C.M.J., Fang, R.H., Luk, B.T. and Zhang, L., 2013. Nanoparticle-detained toxins for safe and effective vaccination. *Nature nanotechnology*, *8*(12), pp.933-938.

Thank You