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Vitamin B12–Assisted Phototherapeutics: A Glimpse of the Future.

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ABSTRACT

Targeting drug delivery has been of interest to several researchers, pharmacologists and clinicians for several decades now. However, despite such intensive work in the field, we have not been able to achieve absolute targeting of drug delivery, thus exposing the unsuspecting patients to several unavoidable adverse effects. With the advent of the new technique known as vitamin B12-assisted phototherapeutics, we might have just taken a right step towards a brighter future: a future without adverse effects. Vitamin B12-assisted phototherapeutic drug delivery modality has the ability to improve the delivery of drugs to a particular site of interest to an extent than ever before, thereby potentially minimizing the emergence of various undesired effects.

Keywords: Targeting, Drug delivery, Cobalamin, Visible light, Cancer, Fluorophore

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THE BASIS

Phototherapeutics, as the name implies, involves the use of light in medicine. More specifically, light is used as an adjuvant to favour the delivery of a particular drug to its desired site of action (in contrast, phototherapy is the use of light as a chief therapeutic agent). In short, it improves the selectivity of delivery of the drug (i.e., a targeted delivery modality). Phototherapeutics can involve the visible light spectrum, the ultraviolet (UV) spectrum or the infrared (IR) spectrum, depending on the wavelength that is employed[1].

Vitamin B12 is chosen as a delivery platform here, because the membrane receptors for B12 have been found to be upregulated in diseased cells, owing to the increase in B12 requirement in these cells for their enhanced rates of growth and multiplication[2]. Further, the molecular structure of vitamin B12 allows for easy addition of drugs and other appendages, without altering the stability of the complex. Most importantly, the bonds that link the peripheral carbon atoms to the cobalt centre of vitamin B12 molecules are photo-cleavable (i.e., they get broken down on exposure to light energy)[3].

THE CONCEPT

In this drug delivery system, the drug of interest (i.e., the drug that is to be administered to the patient) is appended to the vitamin B12 molecule, along with a third entity called a fluorophore[4] (as depicted in Fig.1).

Fluorophores function as antennae (i.e., they receive and transmit signals). Each fluorophore can be set at a particular range of wavelength for its activation. Once a fluorophore is designated with a particular wavelength range, it gets activated only on exposure to that assigned range. It (and hence, the complex) will remain inert at all other wavelengths of light[4].

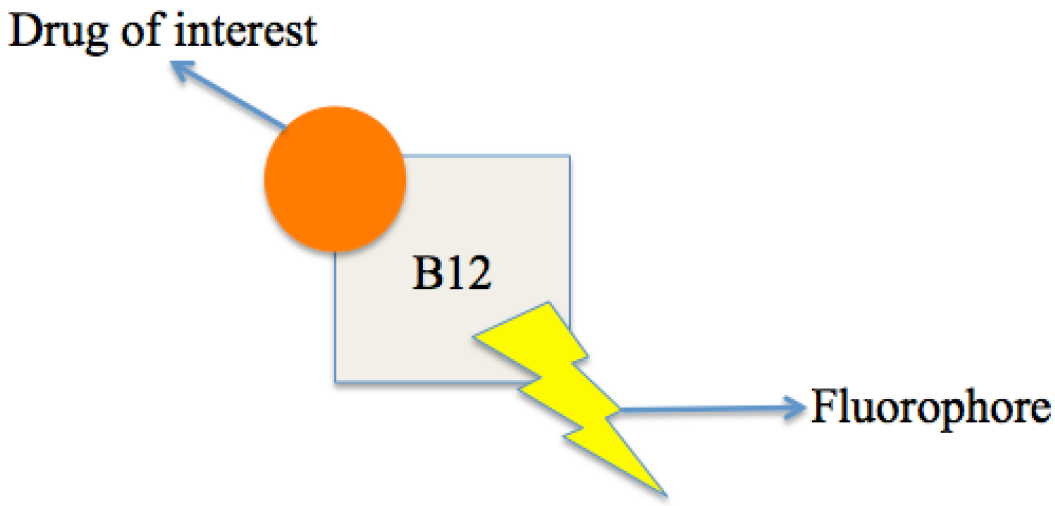

Figure 1: Schematic representation of a typical vitamin B12-based complex, which has 3 components: a B12 molecule, a drug of interest, and a fluorophore.

Once complexes have been made of these three constituents, they are introduced into the bloodstream of the patient (as shown in Fig. 2 and 3). Since they are B12-based complexes, they naturally bind to the B12 membrane receptors (on both normal and diseased cells; but, since the number of receptors on the diseased cells is higher, there is relative selectivity in the binding to the diseased cells). The complexes get internalized into the cells. Following this, the diseased cells are subjected to the light of the previously assigned wavelength range. The rest of the body is kept in total (i.e., kept in absolute darkness) or relative (i.e., kept at a light of a different wavelength range) darkness, so as to prevent these fluorophores (and hence, these complexes) from getting activated[4].

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Once the fluorophores in the diseased area get activated, they transmit the energy to the B12 molecules, which get lysed, thus releasing the drug of interest from the inert complex. Now, the drug is free to perform its function. The complexes in the normal cells (that have not been activated) either get digested by the lysosomal enzymes, or die a natural death along with the cells[4].

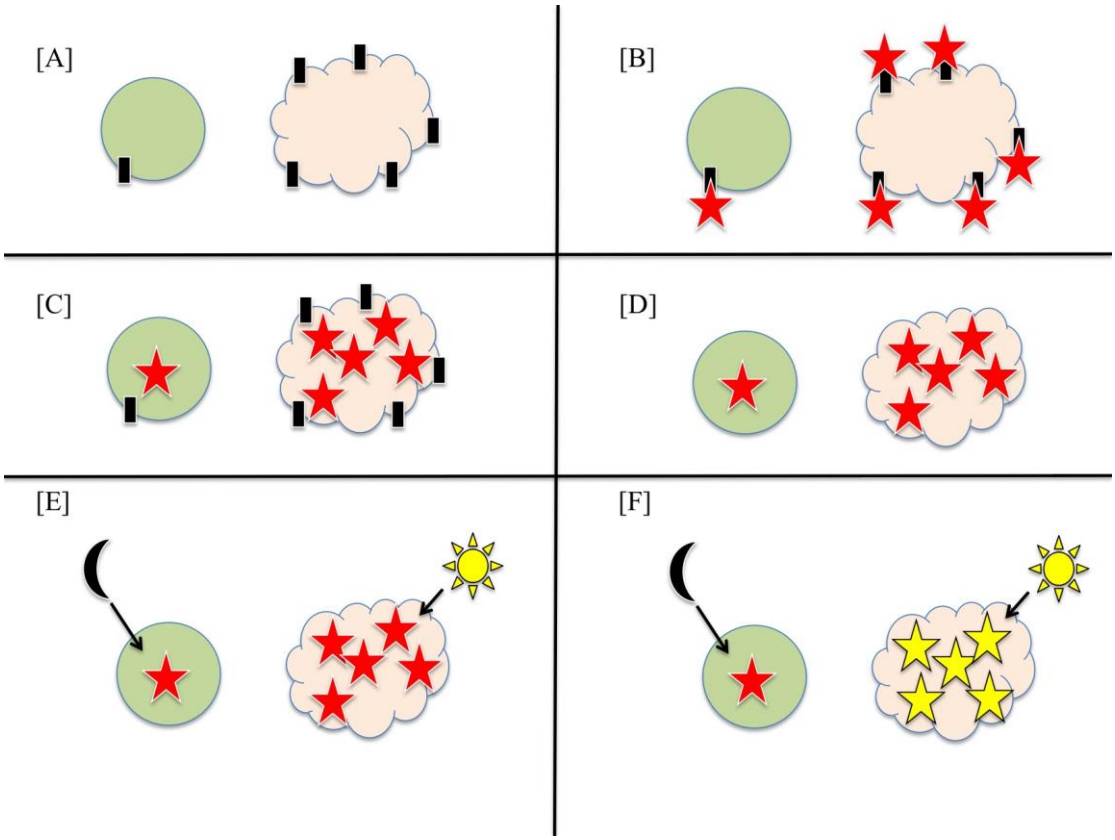

Figure 2: Vitamin B12-assisted phototherapeutics: [A] shows a normal cell on the left and a malignant/inflamed cell on the right; both cells express B12 receptors on their surfaces; [B] shows binding of the injected B12-based complexes onto the surface receptors on both the normal as well as the malignant/inflamed cell; [C] shows internalization of the B12-based complexes; [D] shows internalization of the membrane receptors; [E] shows exposure of the malignant/inflamed cell to light, while the normal cell is kept unexposed to light; [F] shows selective activation of the B12-based complexes in the malignant/inflamed cell, while the complex in the normal cell still remains inactive.

For instance, if a patient has a malignant lesion in his/her left arm (as depicted in Fig. 3), light (of the previously assigned wavelength) will be targeted only on his/her left arm, so that the complexes (made up of vitamin B12, an anticancer agent and a fluorophore) in the left arm get exclusively sensitized, and the cancer cells get destroyed. By avoiding the exposure of other normal cells to the anticancer agent, it is possible to minimize the incidence of adverse effects to a bare minimum. Thus, this modality can make targeting of drug delivery a reality.

ADVANTAGES[4]

- Visible light spectrum (400 to 700 nm) can be used in this technique (thereby avoiding the more expensive and more adverse effect-prone UV or IR spectrum).
- Absolute targeting of drug delivery is experienced, thereby almost nullifying undesired effects.
- It is a common platform for almost every drug in the market.
- It can also be used in combination therapies (by using multiple complexes, each assigned a different range of wavelength) in antimicrobial and cancer chemotherapy.

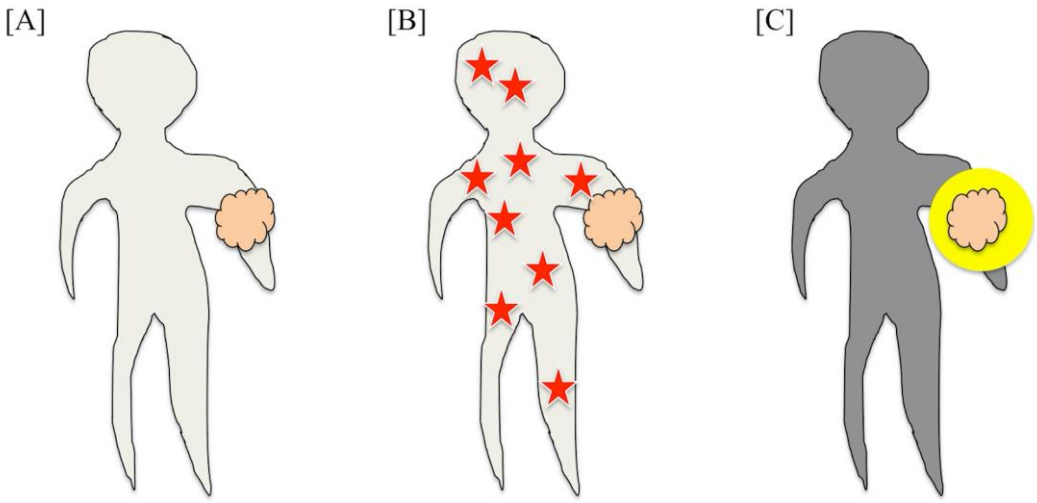

Figure 3: Schematic representation of the clinical application; [A] shows a figurative person with a hypothetical lesion in the left upper limb; [B] shows injection of the B12-based complexes into the bloodstream of the person; [C] shows selective exposure of the lesion to a light source, while the rest of the body is kept in total or relative darkness.

LIMITATIONS

Possible limitations of the concept include the following[4]:

- It may be cumbersome to expose anatomically incongruent sites to light.
- It may not be applicable for lesions in the central nervous system, as the skull will not permit penetration of visible light.
- Adverse effect profile of the fluorophore and vitamin B12 molecules are to be considered.
- Cost of the treatment might be higher than conventional therapies.
- The entire procedure (from manufacturing to dispensing) has to be done with caution, so as to avoid lysis of the complex on exposure to light.
- It may not be an option for drugs that are photo-cleavable on their own, as this may lead to formation of reactive metabolites.

CURRENT STATUS

The concept has not been tested in animal or human subjects, as of now. However, a proof-of-concept study has been successfully completed in an in-vitro simulation model, which has raised hopes among researchers[4]. Only time will tell if these hopes have the potential to get translated to the real life scenario.

CONCLUSION

Vitamin B12-assisted phototherapeutic drug delivery systems might finally be the answer to all the questions that have been plaguing researchers for the past few decades regarding targeting of the action of any drug. If the concept sees the light of the day, it could well be a common delivery platform, for literally any drug, and every drug, making it an attractive option for further research.

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