Advances in Drug Delivery using Cowpea Mosaic Virus (CPMV) Nanoparticles

Laia Herrero Nogareda
Universitat Autònoma de Barcelona, Bellaterra 2015

Universitat Autònoma de Barcelona

Introduction

Specific drug delivery is one of the main objectives of current medicine since side effects get reduced. Virus nanoparticles (VNPs) are a promising drug delivery vehicle as they are small, well-characterized and biocompatible.

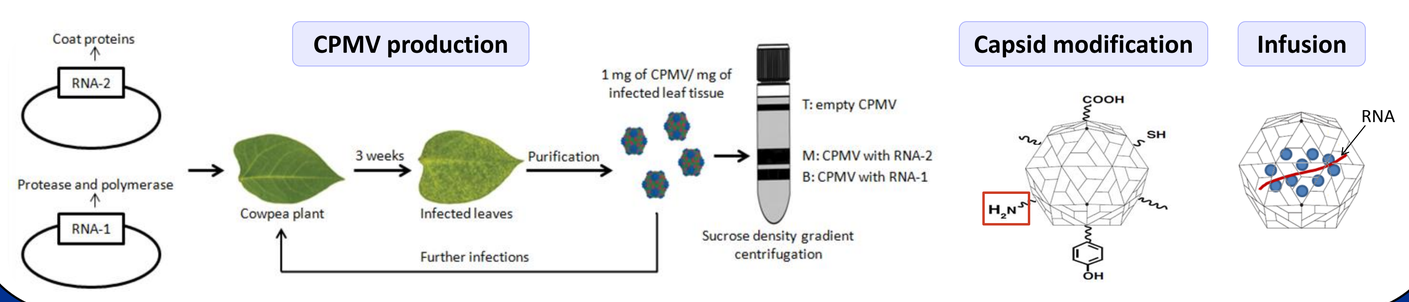
Plant virus like cowpea mosaic virus (CPMV) are interesting VNPs because they are considered non-infectious and nonhazardous in mammals. CPMV is member of family *Comoviridae* and infects the cowpea plant (*Vigna unguiculata*). It has a diameter of 30 nm and a bipartite positive-strand genome.

The methodology of the report was to search for scientific literature in the PubMed database with the aim of understanding what is known about CPMV and discussing how it can help in the treatment of diseases such as cancer.

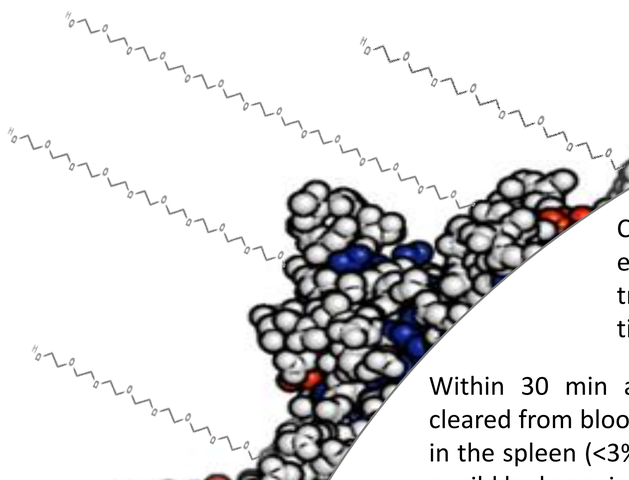
Production and engineering

CPMV genome is formed by two strands, RNA-1 and RNA-2, which are encapsulated separately and are both essential for infection. CPMV production starts with two plasmids that contain respectively RNA-1 and RNA-2.

Once produced, CPMV can be genetically manipulated to introduce mutations. Moreover, different molecules can be chemically linked to the capsid using the reactive side chains of some residues from coat proteins. Infusion can also be used to encapsulate molecules using their interaction with the nucleic acid.



PEG chains

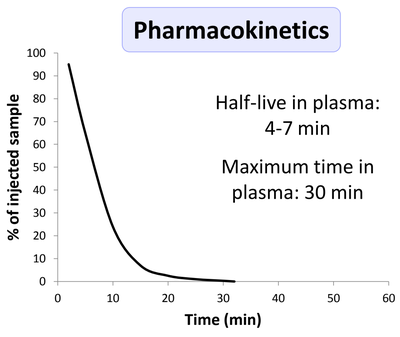


Bio-distribution

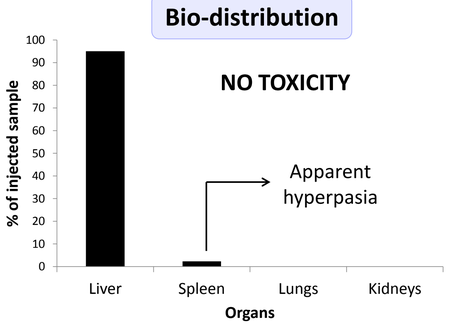
CPMV can be orally administrated since it efficiently traffics from the mice gastrointestinal tract into the system circulation and reach any tissue.

Within 30 min after intravenously injection, CPMV is rapidly cleared from blood circulation and is found in the liver (>90%) and in the spleen (<3%). **No toxicity** is noticed, although mice present a mild leukopenia and an apparent hyperplasia in the spleen.

Pharmacokinetics



Bio-distribution



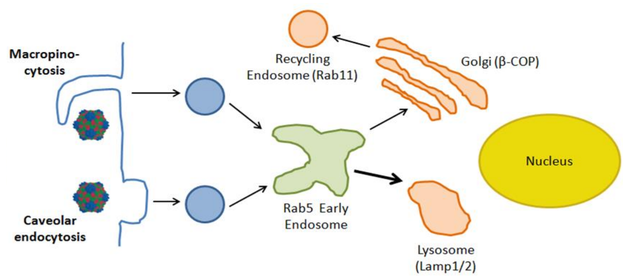
Cell uptake

CPMV recognizes a cell-surface form of **vimentin**. Cytosolic vimentin is a type III intermediate filament, but vimentin has also been found in the surface of:

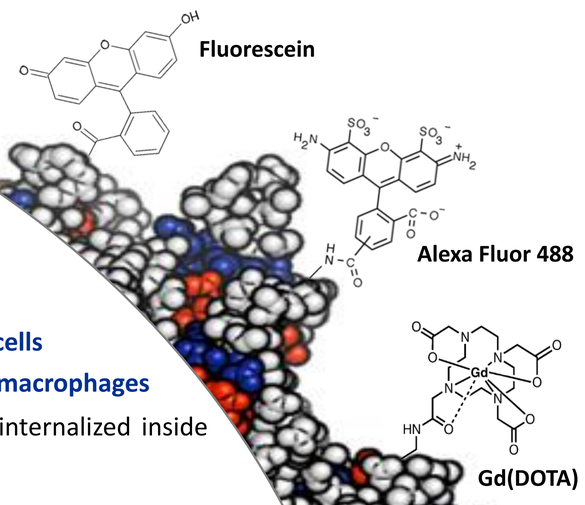
- Endothelial, cervical, colon and prostate **tumor cells**
- Immune system cells, like activated M1 and M2 **macrophages**

After interaction with surface vimentin, CPMV is internalized inside the cell. A PEG coating can inhibit this uptake.

Endocytic uptake and cellular localization



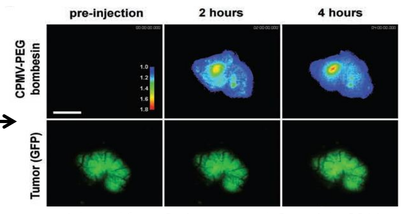
Imaging molecules



Disease treatment

1. **Cancer**: Through vimentin interaction, CPMV targets tumor cells and also M2 macrophages, which are present in the tumor and are involved in metastasis. Moreover, CPMV can be induced to interact with other overexpressed receptors in tumors by linking their corresponding ligand to the capsid:

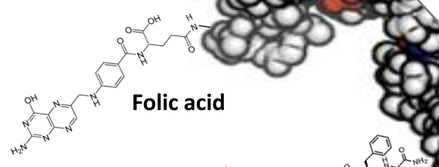
Ligand	Receptor	CPMV uptake
Folic acid	Folic acid receptor	Yes
Bombesin	GRP receptor	Yes
F56 peptide	VEGFR-1	No

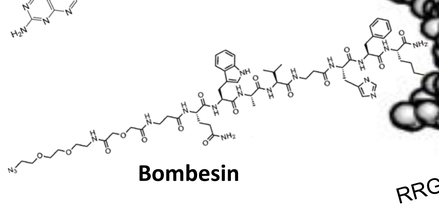


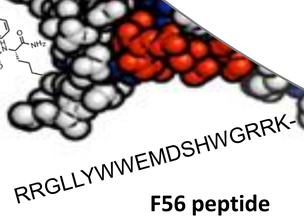
Adapted from Steinmetz *et al.* Copyright 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

2. **Atherosclerosis**: CPMV targets atherosclerotic plaques and M2 macrophages, which are upregulated in atherosclerotic lesions.

3. **Inflammation in the central nervous system** (CNS): CPMV can recognize regions of inflammation and blood-brain barrier disruption in the CNS.



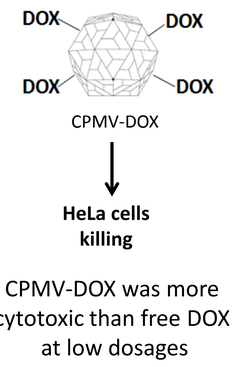




Drug delivery

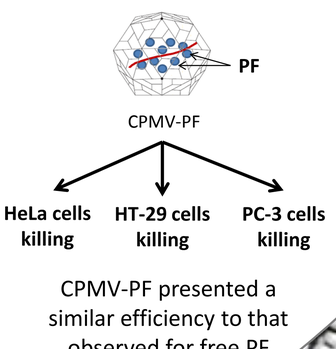
Two experiments from 2013 have shown the efficiency of CPMV as a chemotherapeutic drug delivery vehicle *in vitro*. In both cases, CPMV uptake was due to vimentin interaction and the drug was released in the endolysosome.

Doxorubicin (DOX)



CPMV-DOX was more cytotoxic than free DOX at low dosages

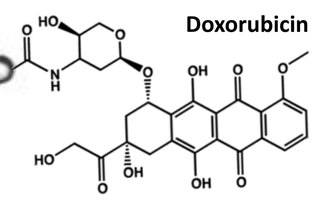
Proflavine (PF)



CPMV-PF presented a similar efficiency to that observed for free PF

DOX and PF: Chemotherapeutic drugs

HeLa: Cervical cancer cells
HT-29: Colon cancer cells
PC-3: Prostate cancer cells
→ Surface vimentin



Ligands

Drugs

Conclusions

CPMV is easily produced and modified, it has a good bio-distribution and results non-toxic. The route of entry to cells expressing surface vimentin is every time more understood.

Drug delivery using CPMV particles could be used in the treatment of cancer, atherosclerosis and inflammation in the CNS, as the nanoparticles can target these regions. However, the efficiency of CPMV as a drug delivery vehicle and the numerous studies about tumor cell targeting have only been carried out *in vitro*.

For this reason, it still cannot be confirmed that CPMV particles would preferably internalize into tumor cells and release their cargo there, avoiding non desirable side effects in the organism. Further *in vivo* analyses could confirm the advantages in drug delivery using CPMV.

References

Koudelka KJ, Destito G, Plummer EM, Trauger SA, Siuzdak G, Manchester M. Endothelial targeting of cowpea mosaic virus (CPMV) via surface vimentin. PLoS Pathog. 2009;5(5):1–10.

Singh P, Prasuhn D, Yeh RM, Destito G, Rae CS, Osborn K, *et al*. Bio-distribution, toxicity and pathology of cowpea mosaic virus nanoparticles in vivo. J Control Release. 2007;120:41–50.

Steinmetz NF, Ablack AL, Hickey JL, Ablack J, Manocha B, Mymryk JS, *et al*. Intravital imaging of human prostate cancer using viral nanoparticles targeted to gastrin-releasing peptide receptors. Small. 2011;7(12):1664–72.

Yildiz I, Lee KL, Chen K, Shukla S, Steinmetz NF. Infusion of imaging and therapeutic molecules into the plant virus-based carrier cowpea mosaic virus: Cargo-loading and delivery. J Control Release. 2013;172(2):568–78.