DENDRIMERS
A NEW WEAPON AGAINST INFLAMMATORY DISORDERS

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INTRODUCTION AND AIMS

Dendrimers are monodisperse, polybranched and polyfunctionalized polymers whose perfectly controlled synthesis affords isomolecular species with an adjusted shape, nanometric size and equal disposition of organic moieties. They are able to enhance both the solubility and permeability of several drugs acting as nanocarriers. However, their particular interest remains in the recent discovery of the biomedical applications that dendrimers display by themselves, with no drugs associated. Hence, the aim of this report is to study a particular case of these innovative molecules, a phosphorus-containing dendrimer with implications in the inflammation process, to finally propose it as a potential treatment of inflammatory disorders as Rheumatoid Arthritis.

STRUCTURE AND CLASSIFICATION OF DENDRIMERS

http://www.andrewschemservices.com/

CORE

- Central initiator platform.
- Its valency determines the branching degree and the final surface group density.
- Small molecules, nanoparticles, other dendrimers.
- Ethylenediamine, N_3P_3, PEO, etc.

INTERIOR BRANCHING

- Robust, covalent structure.
- Generations.
- Connects core to surface groups.
- Chemical nature.

SURFACE GROUPS

- Cationic, anionic, neutral.
- Hydrophobic surface.
- Target-directing groups.
- Multivalent electrostatic interactions.
- Phosphonic acid, glucosamine, carboxylic acid, etc.

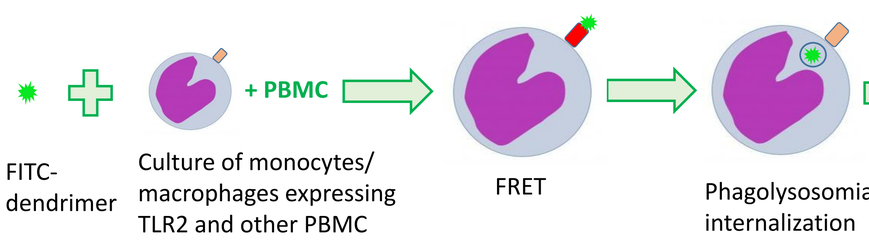
Dendrimer families

All-amine | All-amide | PAMAM | Phosphorus-containing | PEO

THE PHOSPHORUS-CONTAINING DENDRIMER ABP AND INFLAMMATION: STATE OF THE ART

HUMAN MONOCYTES/MACROPHAGES TARGETING AND ACTIVATION

Poupot, M. (2006) *Design of phosphorylated dendritic architectures to promote human monocyte activation*. The FASEB Journal 20, 2339-2351.



http://www.wisegeek.com/what-are-monocytes.htm

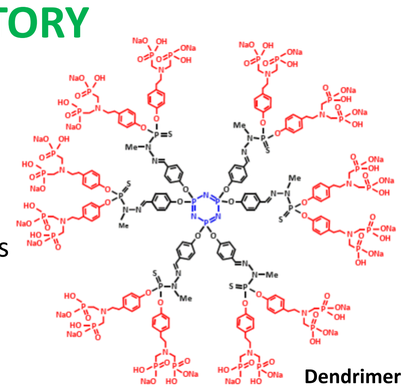
MACROPHAGE ACTIVATION

- Increased size and granulosity
- Changes in surface activation markers

- Phosphonic acid-capped FITC-derived phosphorus containing dendrimers cultured with PBMC.
- FRET showed that TLR2 of the monocyte/macrophage population is stimulated to emit fluorescence by the fluorescent dendrimer.
- Internalization of the fluorescent dendrimer occurred only in the monocyte/macrophage population through a phagolysosomial route. Phosphonic acids are more stable than phosphates and insensitive to phospholipases and phosphatases.
- Macrophage activation measured by morphological and phenotipical changes of these cells.
- Best results of activation and stability given by the Azabisphosphonate-Capped Poly(phosphorhydrazone) dendrimer or dendrimer ABP.

ANTI-INFLAMMATORY EFFECT OF DENDRIMER ABP

Fruchon, S. (2009) *Anti-inflammatory and immunosuppressive activation of human monocytes by a bioactive dendrimer*. Journal Of Leukocyte Biology 85, 553-562.



Monocytes/Macrophages

CLASSICAL ACTIVATION
(INF-γ, LPS, TNF-α mediated)

M1
(expressing IL-1, IL-6, IL-12, IL-13)

- Good APC
- Cytotoxicity
- Inflammation
- Tissue injury

ALTERNATIVE ACTIVATION
(IL-4, IL-10, IL-13 mediated)

M2
(expressing IL-10, TGF-β, PDGF, VEGF, EGF)

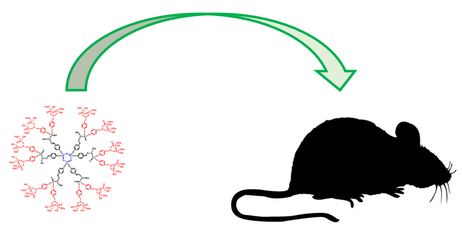
- Poor APC
- Regulation
- Anti-inflammation
- Tissue repair

Dendrimer ABP. Blue: cyclo(triphosphazene) core, black: phenoxy-methylmethylhydrazone branches, red: tyramine based azabisphosphonate groups.
Hayder, M. Et al. (2011) *Anti-inflammatory properties of dendrimers per se*. The Scientific World Journal 11, 1367-1382.

ANTI-INFLAMMATORY AND ANTI-OSTEOCLASTIC PROPERTIES OF ABP IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Hayder, M. (2011) *A phosphorus-based dendrimer targets inflammation and osteoclastogenesis in experimental arthritis*. Science Translational Medicine 3, 81ra35.

Rheumatoid Arthritis (RA) is an autoimmune inflammatory disease that affects approximately 1% of world population. It is characterized by inflammation of the joint synovial membrane mediated by pro-inflammatory cytokines, cartilage degradation by Matrix Metallo Proteases (MMP) and subsequent bone erosion by osteoclasts.



12 weeks of weekly intravenously ABP treatment in IL-1ra$^{-/-}$ mice

Joint inflammation	Cartilage degradation	Bone erosion
• Normal, not swollen synovial membrane. • No infiltration of neutrophils, lymphocytes nor macrophages in the synovial membrane. • Increased secretion of anti-inflammatory cytokines and decreased secretion of pro-inflammatory cytokines.	• Normal cartilage collagen appearance. • Decreased amounts of of MMP-3 and MMP-9 enzymes.	• No osteoclasts presence in the bone matrix. • ABP inhibits the differentiation of monocytes/macrophages into osteoclasts.

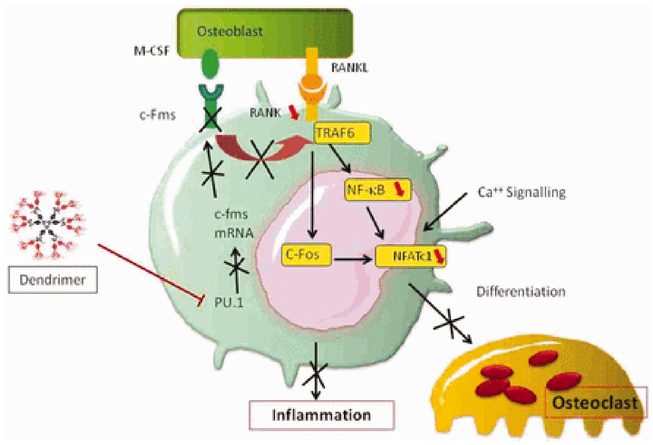
CONCLUSION

DENDRIMER ABP PROPERTIES

IN VITRO
- Monocytes/macrophages targeting through TLR-2
- Phagolysosomial internalization of monocytes/macrophages
- Alternative activation of macrophages: M2 & anti-inflamma-tory response

IN VIVO (RA mice model)
- Inhibits osteoclast differentiation: No bone erosion
- No joint inflammation
- No cartilage degradation

DENDRIMER ABP IS A POTENTIAL DRUG IN THE TREATMENT OF BOTH CHRONIC AND ACUTE INFLAMMATORY DISORDERS



Approximation of dendrimer ABP activity in the inhibition of osteoclast differentiation from a bone marrow macrophage.
Davignon, J.-L. et al. (2013) *Targeting monocytes /macrophages in the treatment of Rheumatoid Arthritis*. Rheumatology 52, 590-598.