Platform Technology for Improving Ocular Drug Delivery

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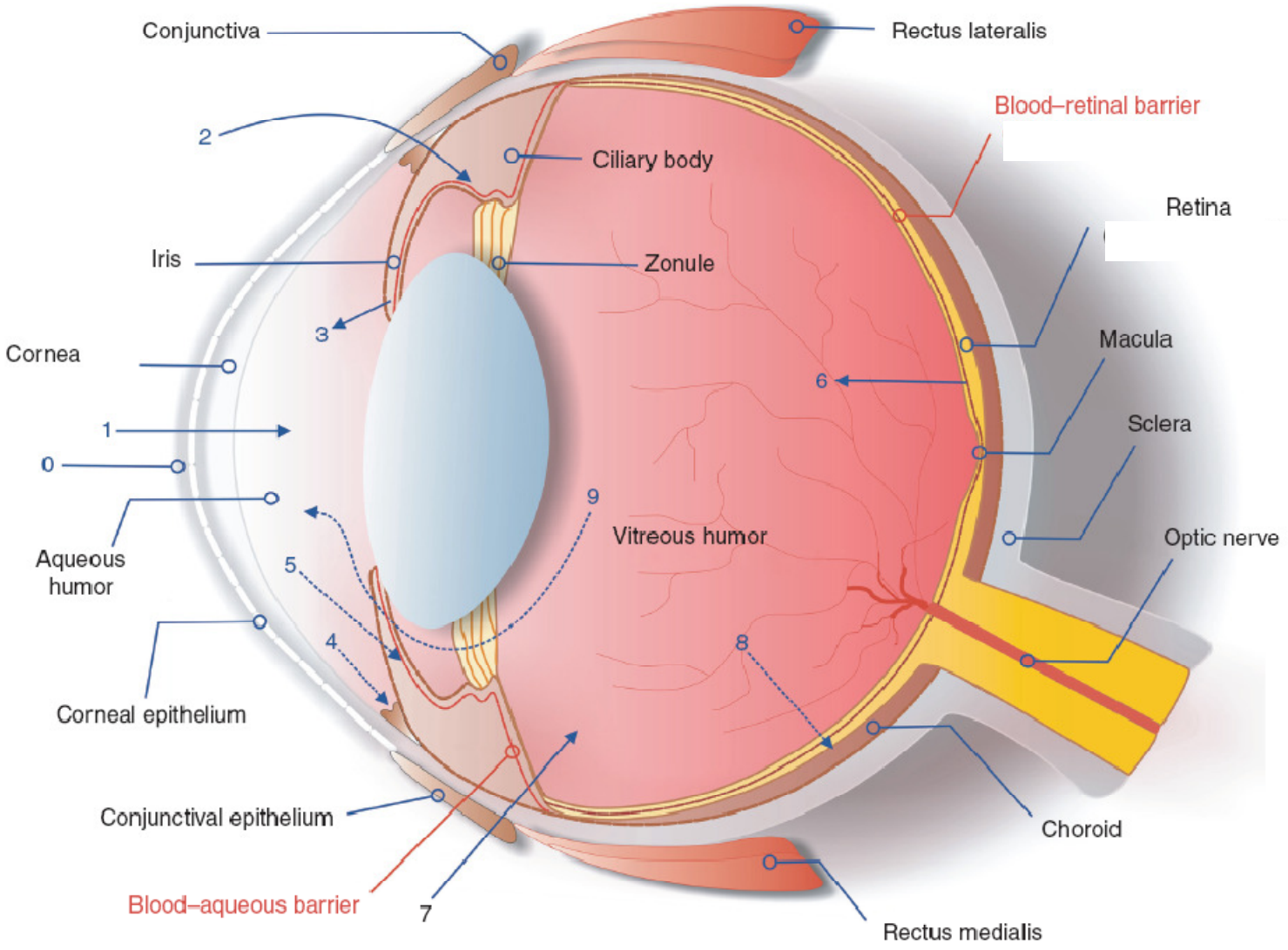
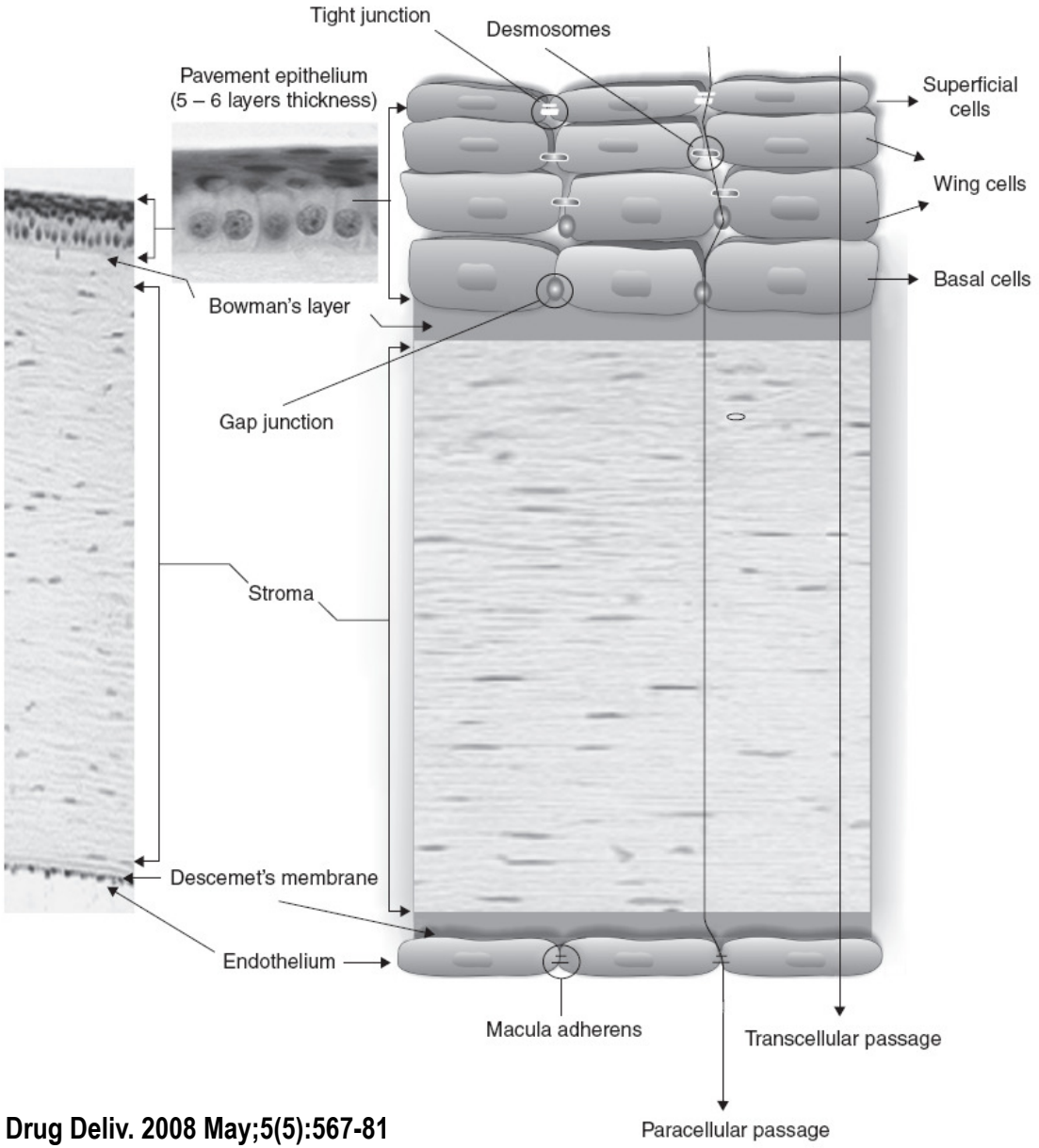
Eye



Barar *et al* Expert Opin Drug Deliv. 2008 May;5(5):567-81

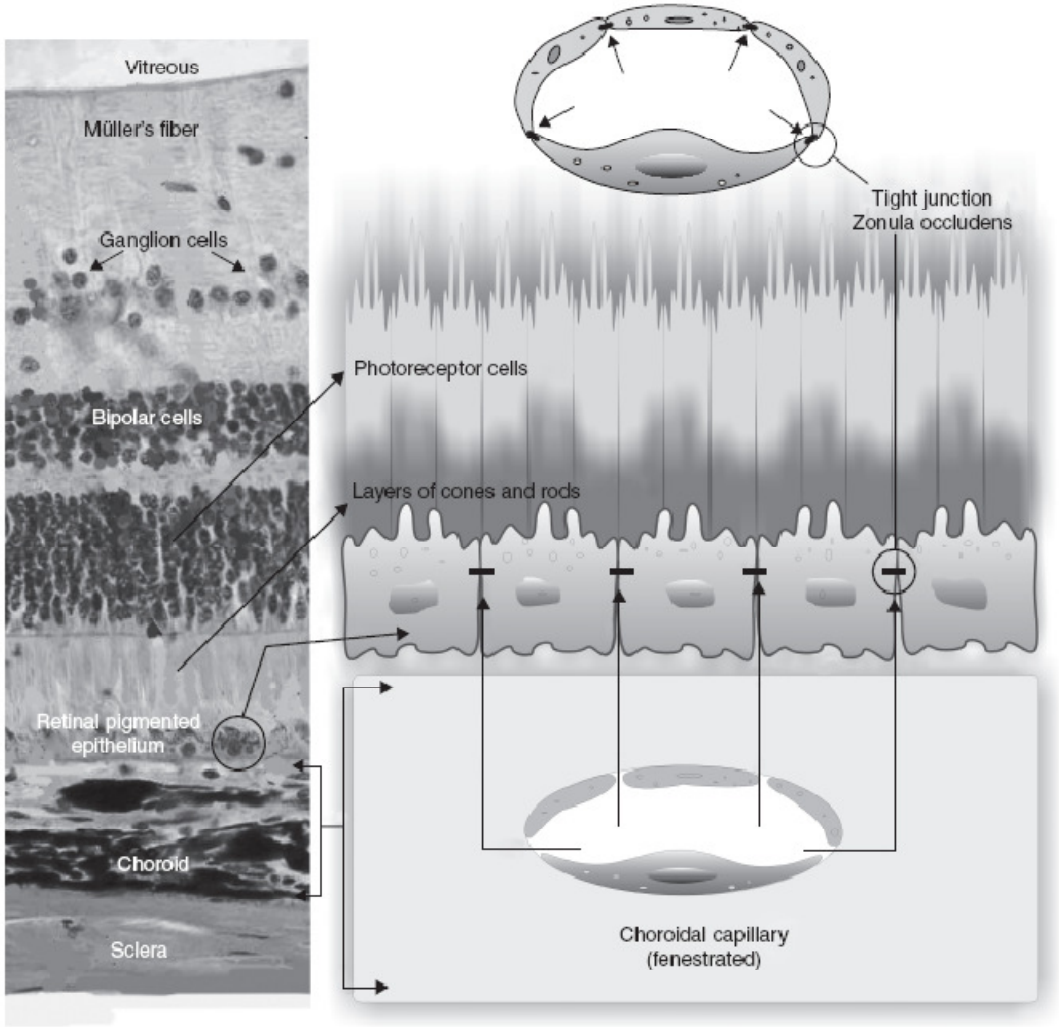
Topical administration to retina: Cornea as a barrier



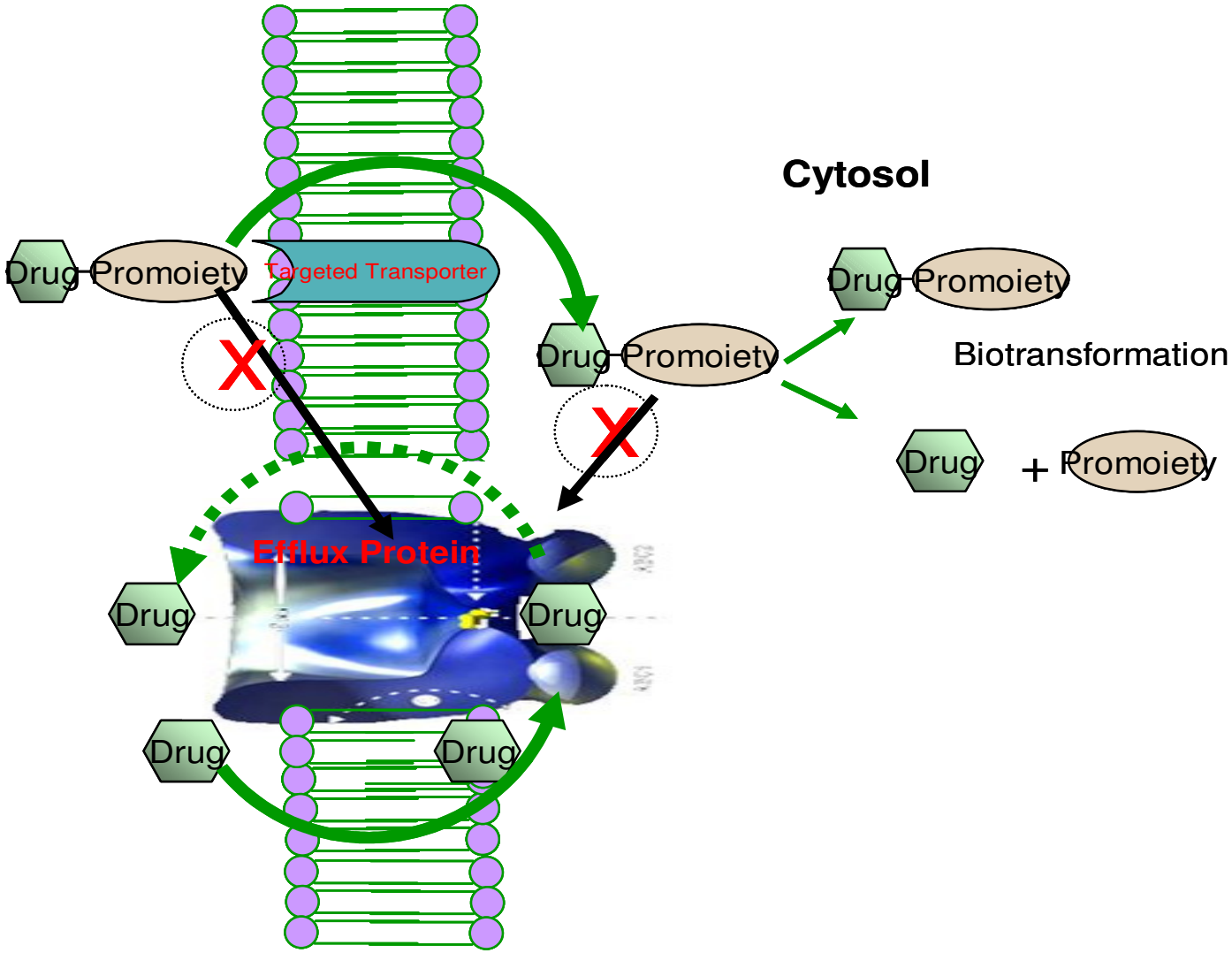
Barar *et al* Expert Opin Drug Deliv. 2008 May;5(5):567-81

RPE as a barrier

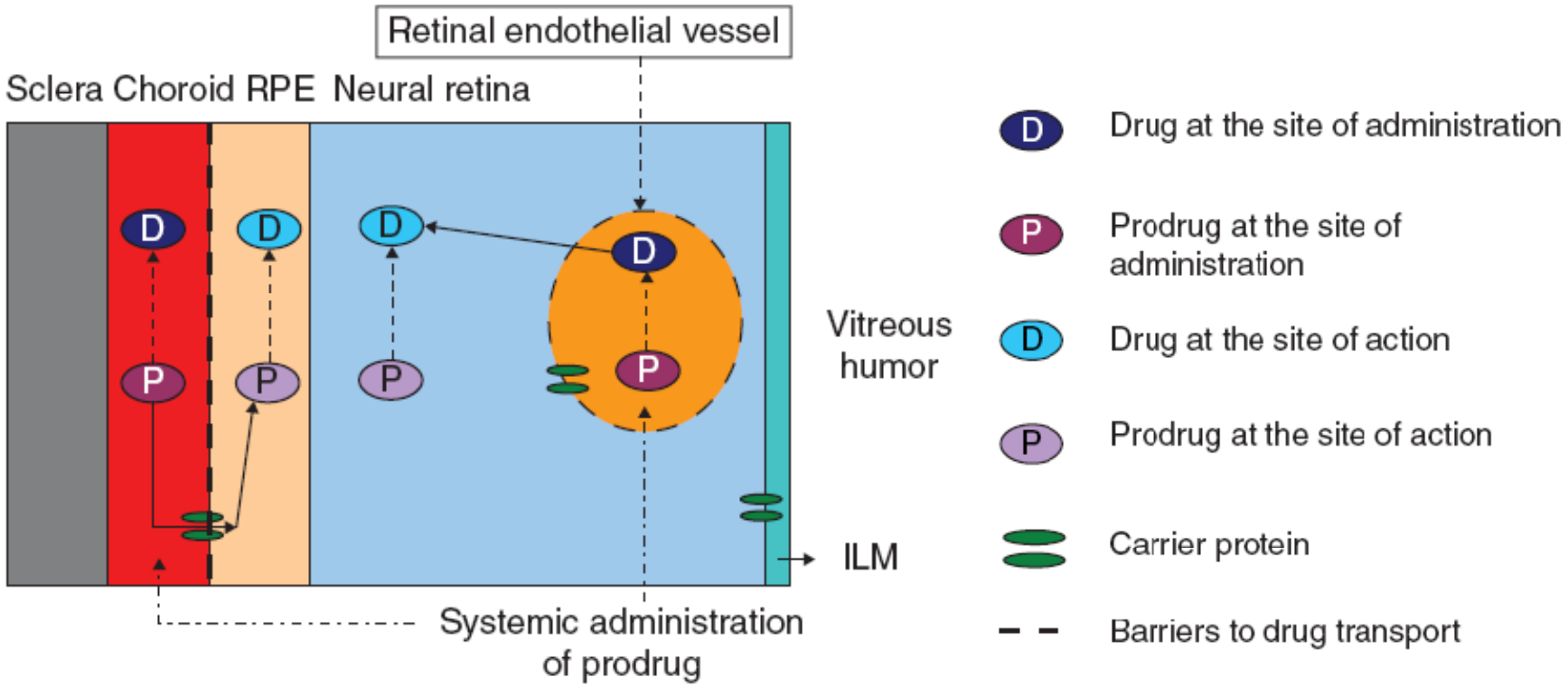
- Blood retinal barrier (oBRB)
  - Formed by the retinal pigmer epithelium (RPE) to limit transport of molecules from choroidal circulation into the retina
  - Tight junctions are expressed between the RPE cells
  - Evidence also suggests the expression of P-gp on the basolateral side of RPE, limiting transport of substances from blood into th eye
- Inner blood retinal barrier (iBRB)



Circumvention of efflux by prodrug derivatization



Transporter targeted drug delivery to retina: systemic administration



D: Drug; ILM: Internal limiting membrane; P: Prodrug; RPE: Retinal pigmented epithelium

Technology

- Present invention provides di- and tri-peptide mono- and di-ester prodrugs which have sufficient physicochemical properties to be formulated into pharmacologically active compositions such as aqueous solutions, e.g., eye drops.

- These compounds can be effectively transported into the ocular tissues by evading the efflux by efflux proteins (e.g., P-gp, MRPs) and utilizing nutrient transporters (e.g., peptide, aminoacid and vitamin trasporters).

- These compounds can effectively reach the anterior segment and/or posterior segment following topical or systemic administrations.

Technology

US007553812B2

(12) **United States Patent**
Mitra

(10) **Patent No.: US 7,553,812 B2**
(45) **Date of Patent: Jun. 30, 2009**

(54) **ACYCLOVIR-PEPTIDE ANALOGS**

(75) Inventor: **Ashim K. Mitra**, Overland Park, KS (US)

(73) Assignee: **The Curators of the University of Missouri**, Columbia, MO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 706 days.

(21) Appl. No.: **10/854,533**

(22) Filed: **May 26, 2004**

(65) **Prior Publication Data**

US 2005/0043246 A1 Feb. 24, 2005

Related U.S. Application Data

(63) Continuation of application No. PCT/US02/38846, filed on Dec. 4, 2002.

(60) Provisional application No. 60/336,666, filed on Dec. 4, 2001.

(51) **Int. Cl.**
A61K 38/16 (2006.01)
A61K 38/00 (2006.01)

(52) **U.S. Cl.** **514/8**; 424/1.69; 514/2

(58) **Field of Classification Search** 514/8
See application file for complete search history.

(56) **References Cited**

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7,214,664	B2	5/2007	Mitra et al.	
2006/0135438	A1	6/2006	Mitra et al.	

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(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

Dipeptide and tripeptide ester derivatives of acyclovir and its analogs are disclosed which are useful to treat herpes virus infections. Also disclosed is a method for preparing a therapeutic agent for targeted delivery to ocular tissue comprising linking the therapeutic agent to one or more groups of the formula -X-Y-$Z_{(n)}$-R; wherein each X, Y and Z is independently Met, Val, Thr, Tyr, Trp, Ser, Ala or Gly; each R is independently H or an amino-protecting group; and each n is independently 0 or 1.

26 Claims, 18 Drawing Sheets

Technology

US007214664B2

(12) **United States Patent**
Mitra et al.

(10) **Patent No.: US 7,214,664 B2**
(45) **Date of Patent: May 8, 2007**

(54) **PEPTIDYL PRODRUGS THAT RESIST P-GLYCOPROTEIN MEDIATED DRUG EFFLUX**

(75) Inventors: **Ashim K. Mitra**, Overland Park, KS (US); **Soumyajit Majumdar**, Oxford, MS (US); **Ritesh Jain**, Kansas City, MO (US); **Yasser Nashed**, Thousand Oaks, CA (US)

(73) Assignee: **The Curators of the University of Missouri**, Columbia, MO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/285,754**

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(65) **Prior Publication Data**

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(51) **Int. Cl.**
A61K 31/00 (2006.01)

(52) **U.S. Cl.** **514/19**; 540/557

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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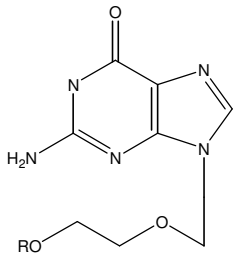
Primary Examiner—B. Dell Chism
Assistant Examiner—Hemant Khanna
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg, Woessner & Kluth P.A.

(57) **ABSTRACT**

Dipeptide, and tripeptide and tetrapeptide ester derivatives of bioactive agents are provided wherein the parent agents are substrates effluxed by the P-gp transporter. The derivatives are useful in treating the same condition as the bioactive agent. Also disclosed is a method for preparing a bioactive agent for targeted delivery by nutrient or peptide transporters comprising linking the agent to one or more groups of the formula —X—$Y_{(n)}$-$Z_{(n')}$-Z'$_{(n'')}$-R; wherein each X, Y, Z, and Z' is independently Met, Val, Thr, Tyr, Trp, Ser, Ala or Gly; R is independently H or an amino-protecting group; n=1, and each, n', or n" is independently 0 or 1.

9 Claims, 9 Drawing Sheets

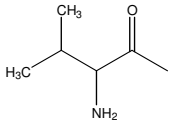
Structures



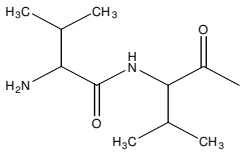
Acyclovir

R-promoiety

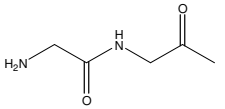
Substitutions of R:



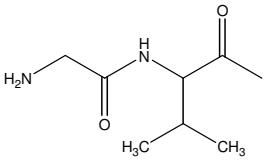
Valine



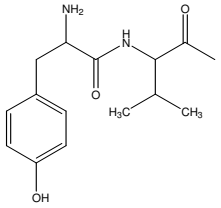
Valine-Valine



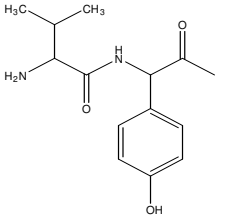
Glycine-Glycine



Glycine-Valine

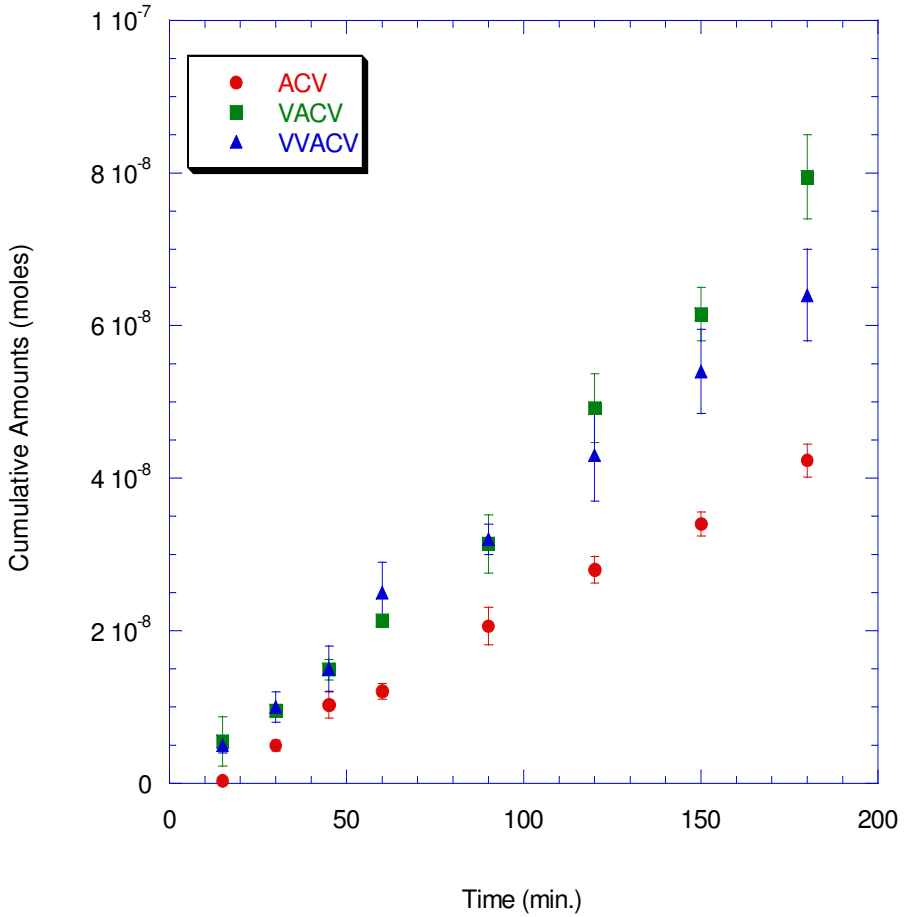


Tyrosine-Valine



Valine-Tyrsoine

Time course of corneal permeation of cumulative amount of ACV, L-Val-ACV, VVACV across rabbit cornea.



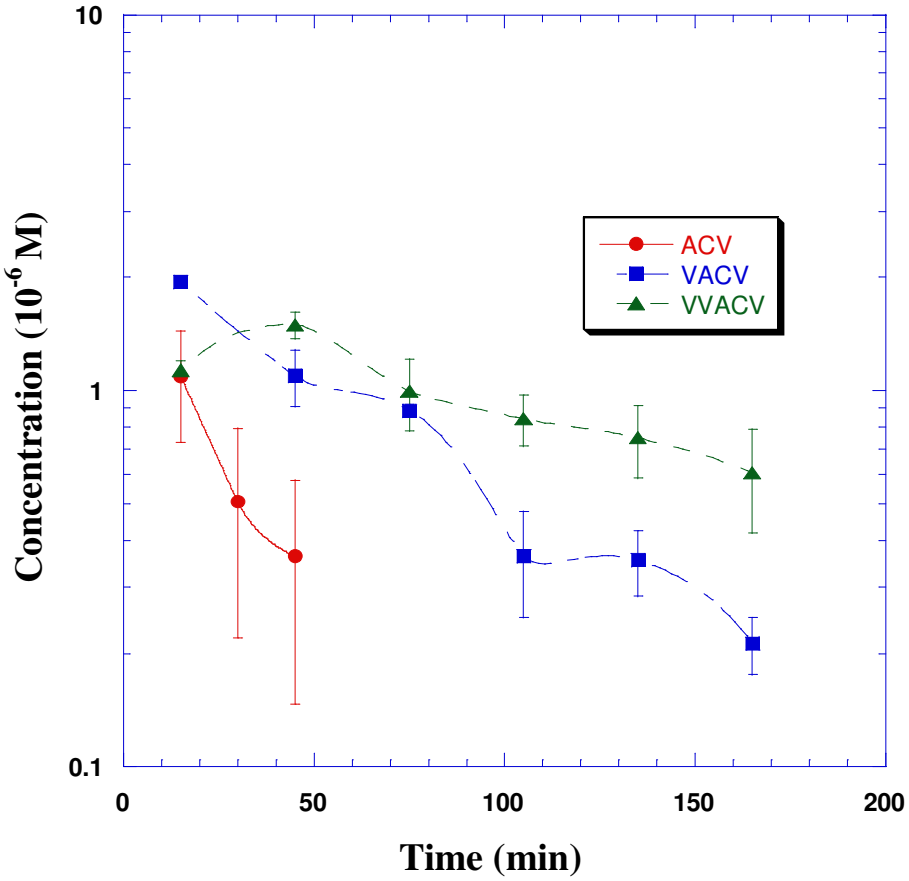
Transport Characteristics of Prodrugs

Drug	P_{app} * 10^6 cm/sec (± S.D)
ACV	4.24 (± 1.41)[a]
VACV	12.1 (± 0.44)*
VVACV	9.91 (± 2.40)*
GVACV	12.4 (± 1.42)*
YVACV	7.19 (± 1.38)*
VYACV	8.34 (± 1.12)*

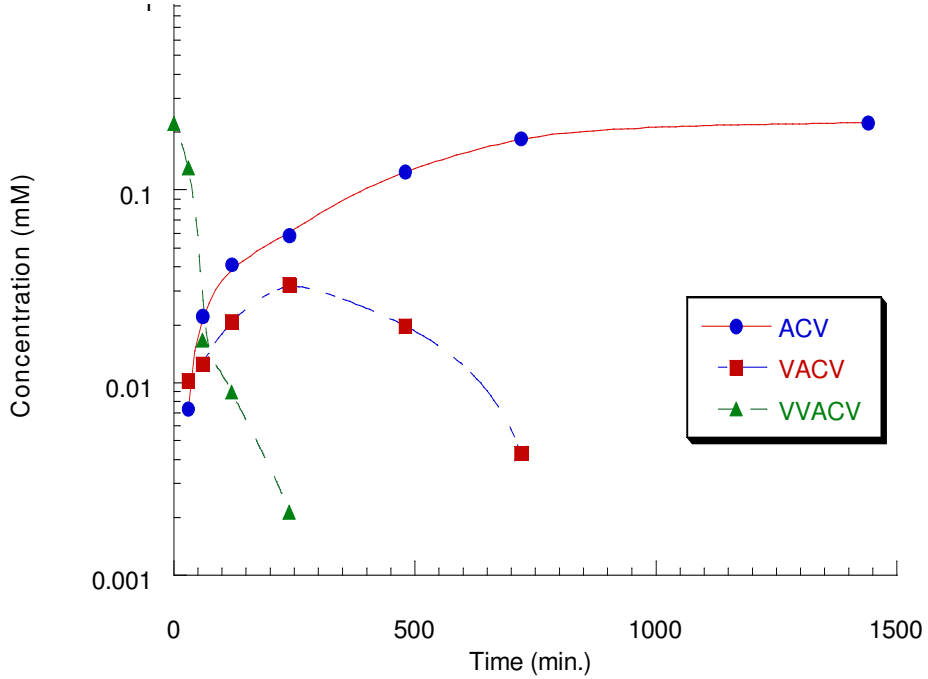
[a] control

* $p<0.05$

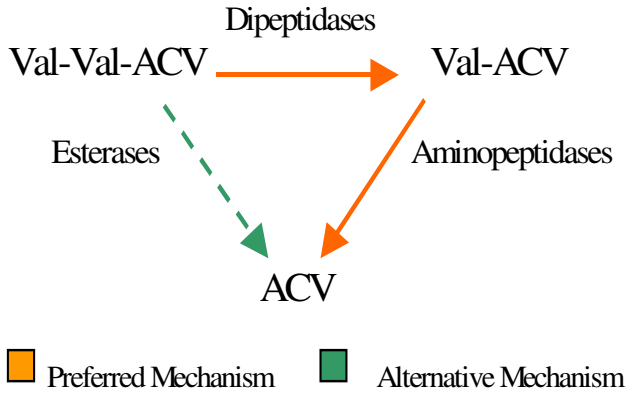
Anterior chamber levels of ACV following systemic administration of ACV, VACV, and VVACV



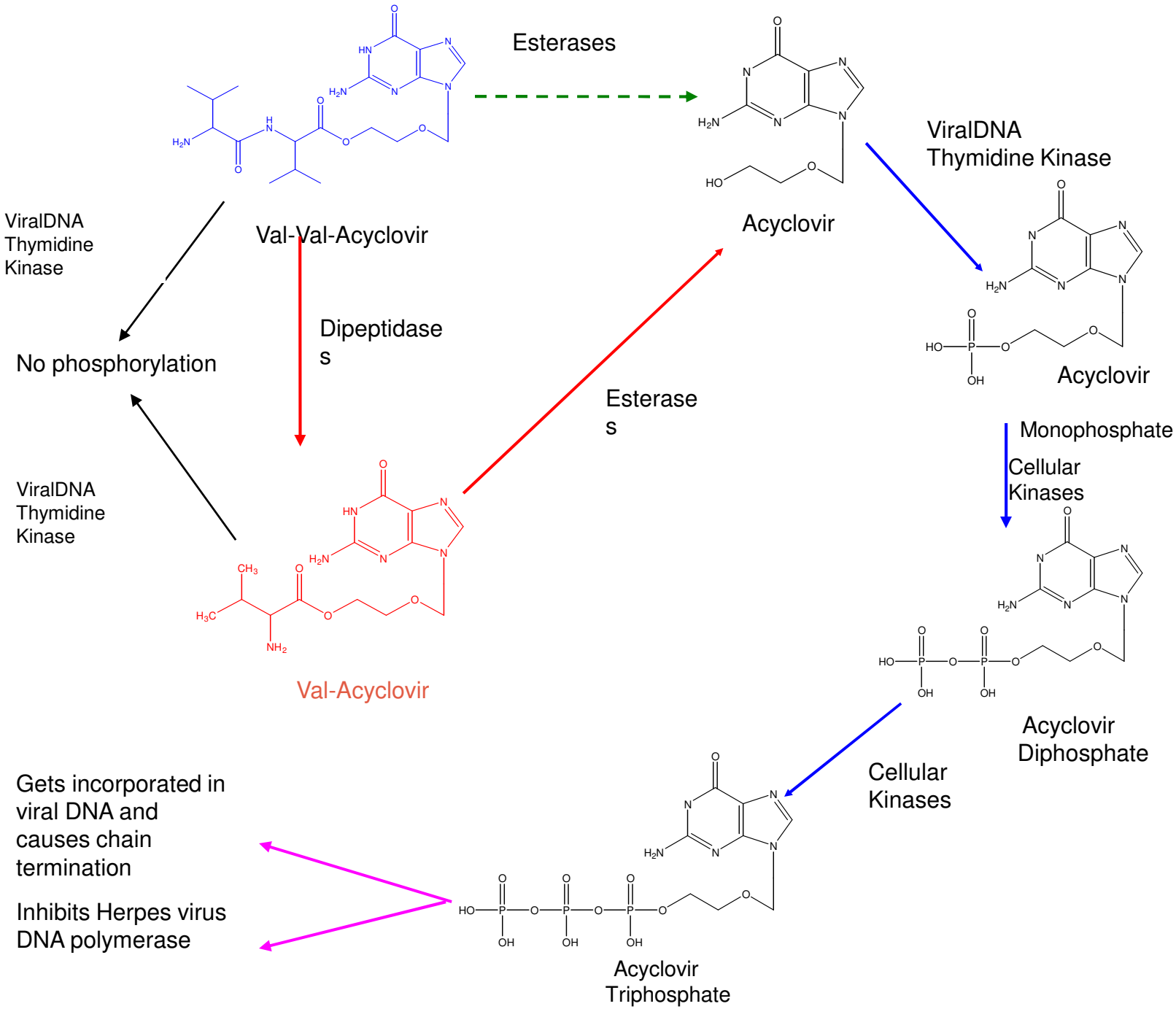
Regeneration of the Prodrug



Regeneration of ACV from Val-Val-ACV upon subsequent hydrolysis to VACV in isolated rabbit cornea



Possible mechanisms of enzymatic hydrolysis of di-peptide prodrug, Val-Val-ACV to Acyclovir in cornea. Val-Val-ACV prodrug is sequentially hydrolyzed via Val-ACV to yield the parent drug ACV. The hydrolysis is mainly enzymatic and not chemical as Val-Val-ACV is relatively more stable in IPBS (pH 7.4, $t_{1/2}$ ≈108 hrs.)


Esterases
Val-Val-Acyclovir
Acyclovir
ViralDNA
Thymidine
Kinase
ViralDNA
Thymidine Kinase
No phosphorylation
Dipeptidase
s
Esterase
s
Acyclovir
Monophosphate
Cellular
Kinases
ViralDNA
Thymidine
Kinase
Val-Acyclovir
Acyclovir
Diphosphate
Cellular
Kinases
Gets incorporated in
viral DNA and
causes chain
termination
Inhibits Herpes virus
DNA polymerase
Acyclovir
Triphosphate

Stereoisomeric prodrugs of ACV

- Systemic drug delivery (intravenous or oral) is potentially an effective route to treat various systemic as well as ocular disorders. However, drugs administered by this route must cross the intestine to reach the systemic circulation and subsequently the blood ocular barriers (BOB) to reach the inner ocular tissues.

- Limited therapeutic efficacy of ACV against herpes infections following oral administration is due to its poor permeability across oral mucosa. Several studies proved that oral bioavailability of ACV can be improved by prodrug derivaization.

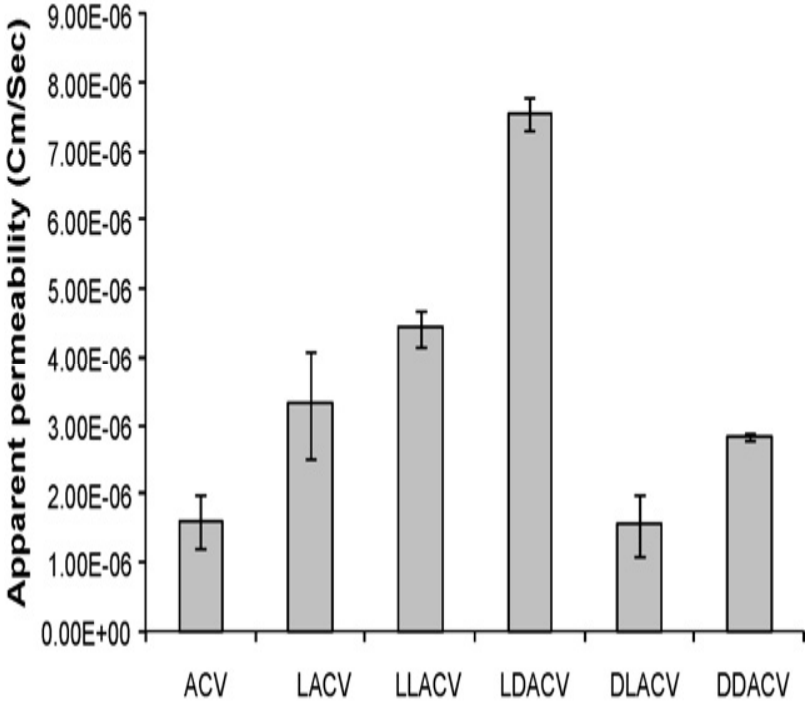
Stereoisomeric prodrugs of ACV

- Amino acid and dipeptide prodrugs of ACV that have been evaluated before were found to be metabolized rapidly and completely to the parent drug during first pass following oral administration.

- However, regenerated ACV has to cross Blood Aqueous Barrier (BAB) to permeate into the anterior chamber ocular tissues. So there is a necessity to design prodrugs such that their hydrolytic rate can be modulated to generate higher amounts of intact prodrug in the systemic circulation resulting from improved oral bioavailability.

- Hence we synthesized stereoisomeric dipeptide prodrugs of ACV (L-val-L-val- ; L-val-D-val- ; D-val-L-val-; D-val-D-val-)

Stereoisomeric prodrugs of ACV

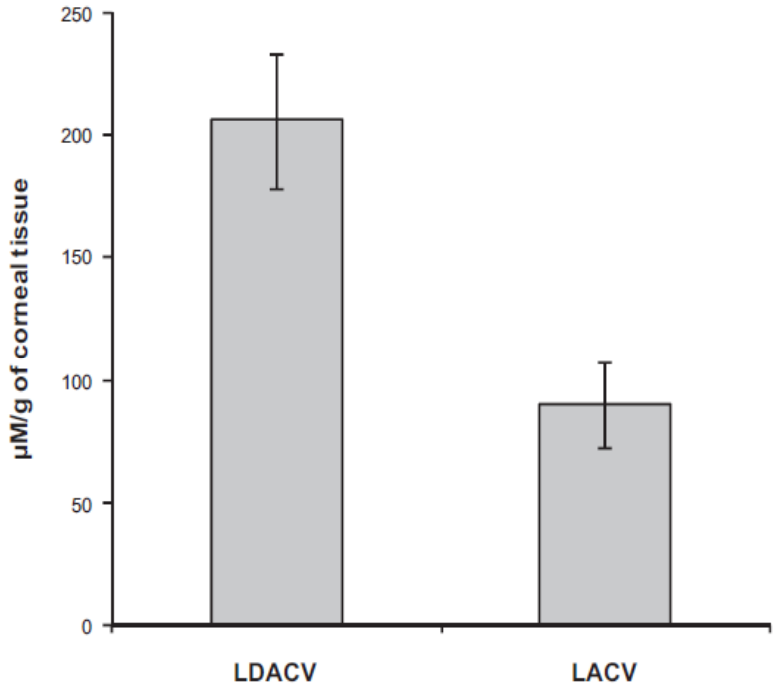


Apparent permeability of ACV Stereoisomeric prodrugs across Caco-2. Each value is represented as mean±S.D. (*n = 4).*

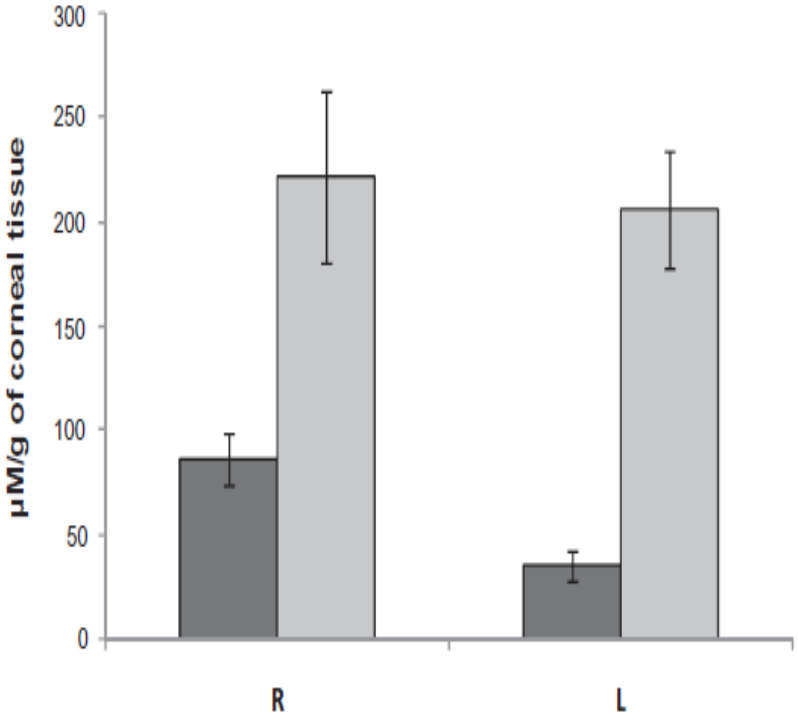
Drug	K×10^3 (h^{-1})	$t_{1/2}$ (h)
LL-ACV	-	<0.08
LD-ACV	688.23 ± 48.68	1.01±0.07
DL-ACV	110.06 ± 4.52	6.27±0.25
DD-ACV	ND	ND

Stability of ACV prodrugs in rat intestinal homogenate— first-order degradation rate constants and half lives of all prodrugs.
"ND" Represents no degradation during the time of study. Symbol "–" represents the whole prodrug degraded in less than first sampling time point (5 min). Each value is represented as mean±S.D. (*n = 3).*

Corneal absorption of ACV prodrugs following oral administration



Corneal uptake of ACV following oral administration of LDACV and LACV in rats. (Each value represents mean ± SD).



Corneal concentrations of LDACV and ACV following oral administration of LDACV at a molar dose equivalent to 30 mg/kg of acyclovir in rats (■-ACV, ■-LDACV). Values are represented as mean ± SD, n = 3–4) [R-right eye, L-left eye].

Conclusions

- The dipeptide prodrugs of ACV were highly permeable across cornea as compared to ACV.
- Studies conducted in our laboratory have shown that these dipeptide ester prodrugs are less toxic (no cytotoxicity detected within the concentration range studied) as compared to TFT and ACV.
- The dipeptide prodrug Val-Val-ACV has also shown excellent in vivo activity against rabbit stromal keratitis, which is not adequately treated by current antiviral therapeutic regimens. Val-Val-ACV has been shown to be as efficacious as TFT at a much lower molar concentration in the rabbit stromal keratitis model.
- The stereoisomeric prodrug L-val-D-val-ACV exhibited good enzymatic stability and improved ocular absorption following oral administration.
- This technology can be utilized to improve ocular bioavailability of various drugs following both topical and oral administration in order to treat several ocular infections and disease conditions.

Thank you

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Questions