

UC Berkeley

UC Berkeley Electronic Theses and Dissertations

Title

2', 3', 4'-trihydroxychalcone is an Estrogen Receptor Alpha Coagonist

Permalink

<https://escholarship.org/uc/item/98d3s49d>

Author

Herber, Candice Blair

Publication Date

2014

Peer reviewed|Thesis/dissertation

2', 3', 4'-trihydroxychalcone is an Estrogen Receptor Alpha Coagonist

By

Candice Blair Herber

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Endocrinology

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Dale C. Leitman, Co-Chair

Professor Gary L. Firestone, Co-Chair

Professor Jen-Chywan Wang

Professor Joseph L. Napoli

Spring 2014

¶ ¶ ¶ 7+& IRU KRXUV ZLWK GRRHVERWKKDVLZBQQG WROO
VDPH WLPH)XQFWLRQDO DQDO\VLRI XHVLWUJDGJL RQ H EQLQG
DQRWKHU (5. ELQGG¶QJ¶ F7+&OFRHPR QVWUWHWUHG WIKDQV FRPSOH
RI HVWUDGLRO DQG ¶ ¶ ¶ 7+& MQQ(5UJLLW SRFVDFEVLHY D'WV
UHJXODWHG JHQHV LQ 8 26. FHOOV & VDIQG FRPVEU DQ WLRQ G IRG
SUROLIHU DWLRQ RI 0&) FHOOVEQR FVNIKIG VIDVWU D'GIDROO/ LQ C
SKDVH FHOO F\FOH WUDQVLWLRQVZUWJKRQDWEIFGREN HQWSD B
RYDULHFWRPLJHG PLFH RQ D VR\ IUN#5,FkrRzupGLHW WUHQ W
7+& GLG QRW FDXVUDWWRHQ LQHG SEJROFNIHGG HSUWUOLGH B DWLLR
H[SUHVVLQR \$OWKRXXK ¶ ¶ ¶ 7+&V EIORQ NLHG XHWHWU LQGL
UHJXODWHG DQG PRGXODWHG HVWUDGLRQDFDQGMFHG JHQH
GLVSOD\V XQLTXH FRDJRQLVW DFVSLYRLW\HWKURIXRQ (5WZRLMK
IXWXUH +57 DQG H[SDQB LQ5. RXHU XQDFXORHGDQHG UO E WLRQ

, Q GHGLFDWLRQ WR -DPHWD%ODL:UODGXPDRPOTDLRL
ZKR WDXJKW PH WR DEHQWKYH LPSRQWIDGSHRUVSIVULDRQ F
7KLV RQH LV IRU ERWK RI \RX

7\$%/(2) &217(176

&KDSWHU 2QH

/LWHUDWXUH 5HYLHZ DQG ,QWURGX

RJ\ DQG 3XEHUWW U R J

RJ\ LQ (WKHV%UDWQ U R J

RJ\ LQ (WKHV%RQW U R J

RJ\ LQ (\$GLSRVH WLVVXH R J

(V W U R J

3 K D U P D

QJ QHZ 6(5Q6 IRG +57H Q W L

5 H I H U H

&KDSWHU 7ZR

0DWHULDOV DQG 0HWKRGV

5 H I H U H

& K D S W H U 7 K U

& K D S W H U) R X

LL

& R Q F O X

5 H I H U H

LLL

/,67 2)), * 85(6

)LJXUH)ORZL QK D&UCVD &RLPFSDDU DDQ GO HI W/KHRC V6 F U H H Q L

)LJXUH \$ F W W Y E V & K B I O 6 F Q Q W H V H R Q (5 .

)LJXUH & R I D W R Q R L V W \$ F W L Y 7 + (& R Q (5 . D Q G

)LJXUH 6 \ Q H U J A & R Z L W K V W W U R R Q H D Q G (V W U L

)LJXUH ¶ ¶ Q J ¶ W K + & / % L Q R G L (5 . D Q G (5

)LJXUH & R I D W R Q R L V W \$ F W L Y 7 + & R Q . 5 7

)LJXUH & R P S D U L V R Q R I ¶ ¶ ¶ H J X O D W H G R Q (5 0 6 R

)LJXUH 7 L P I Q & B X U , Q H G R F W L R Q . R Q . 5 7 D Q G 1

)LJXUH * O R X E O D W * L H Q Q E \ H ¶ ¶ W U D G E & O S O X V (V

)LJXUH & R P S D G L R Q Q D R I G H ¶ W ¶ H ¶ H J X O D W * L H R Q

)LJXUH 5 7 3 & 5 R I & O D V V , , , 5 H J X O D W H G * H Q H V

)LJXUH (5 . L V & S H T V X L U , H G Q I Q X F W Q R Q J D Q G * H Q H

)LJXUH 0 R B F I O D R I L W K H R I O * H Q H 6 \ Q H U J \

)LJXUH 5 H F U X D W G P G Q W R W R W K W H 5 7 3 U R P R

)LJXUH (5 . 3 U R W S K I R O \ D O O V B R Q 6 ¶ W D W S H Z L W K ¶

)LJXUH 0 R G H O R I (5 . + H W H U R O L J D Q G

)LJXUH (I I H F W + & R I (¶ R Q ¶ (5 . ¶ % ' 0 X W D Q W V

)LJXUH) X Q F W E R I O W H O R E V J D Q G & R P S O H [

)LJXUH * H Q H W Q Z L X F K V L R Q ¶ K W ¶ U D + & L S O X V (V

)LJXUH , Q B W R D V % I G Q (G L V Q U D W R ¶ (5 + & Z L W K ¶ ¶

)LJXUH 0 R G H O R I (V W W E G B R Q J * H Q H 5 H J X O D W L R Q

)LJXUH 5 R O E % U (H D W W R & B Q F M L R Q H O O 3 U R O L I H U D

)LJXUH ¶ ¶ Q J ¶ W R + (5 % L Q G L &) & H O O V

)LJXUH ¶ ¶ L Q U 7 + & V % D O R I F R O H U Q W X R I Q G 3 U R O L I

)LJXUH ¶ ¶ L Q U 7 + & V % D O R I F R O H , Q G X F H G 6 3 K D V

)LJXUH ¶ ¶ J X O D W L R Q H L Q H O &) & H O O V

)LJXUH

¶ ¶ L Q T U 7 7 & V % D O R I F R N C H , Q U R X G E H I G I S D M M I U R Q

)LJXUH

¶ ¶ V W U T D & L S O X M I F E W V X R H Q : H K J K L W H

)LJXUH

¶ ¶ L Q T U 7 7 & V % D O R I F R N C H , Q H C Q H F V H G 8 W H U L Q

)LJXUH

¶ ¶ I J V T O & Q G O R P P H N W L Q U D O & H O O 3 U R O L I H U

)LJXUH

¶ ¶ W L Q J & (V W R G X G D S R O V H H Q I H W X G \$ G L

/,67 2) 7\$%/(6

7DEOH

7KUHIX&ODWVGIVHRQH5&ESOXV (VWUDGLRO

7DEOH

(5. %LQGLQJ \$IILQLW&KVDOR(QWUDGLRO DC

/,67 2) \$%%5(9,\$7,216

*Q5+ JRQDGRWURSLQ UHOHDVVLQJ KRUPRQH

/+ OXWHLQL]LQJ KRUPRQH

)6+ IROOLFQHVWLPXODWLQJ KRUPRQH

+3* K\SRWKD\WDPULFJBRQWQDO D[LV

003V PDWUL[PHWDOORSURWHLQDVHV

337 7ULV QRKOGURS[USKSHO + S\UD]ROH

,/ LQWHUOHXNLQ

,/ LQWHUOHXNLQ

71) WXPRU QHFURVLV IDFWRU

,)1 LQWHUIHURQ JDPPD

7*) WUDQVIRUPLQJ JURZWK IDFWRU EHWD

33\$5/ SHUR[LVRBHD\$WRQDMH@WRIFHSWRU GHOW

7* WULJO\FHULGH

65 & VWHURLG UHFHSWRU FRDFWLYDWRU
65 & VWHURLG UHFHSWRU FRDFWLYDWRU
65 & VWHURLG UHFHSWRU FRDFWLYDWRU
& % 3 F\$03 UHSPHQLQJ SURWHLQ
1 & 25 QXFOH DU UHFHSWRU FRUHSUHVVRU
3, . SKRVSKDWLG\OLQRVLWRO NLQDVH
\$.7 SURWHLQ NLQDVH %
0\$3. PLWRJHQ DFWLYDWHG SURWHLQ NLQDVH

\$ & . 1 2 : / (' * (0 (1 7 6

, ZRXOG OLNH WR VWDUW RXW E\KW KDRQNL Q Q @ \VIX\$S\$RUV WR,U D
WR IROORZ P\ GUHDPV DQG P\ SXU VXLGW I R U H K E B K M U D H F G X Q R Z V
PRP DQG KHU FUHDWLYH VSLULWHI B Q @ W Z H D \ F K I L L O J O E @ J W K \ H O D
DQG FUHDWLYLW\ ORP \RX ZHUH DVOZYD V D V @ H O R Y L R Q U P H D U Z L
, DP WUXO\ JUDWHIXO 'DG WKD S R U W R X Q I R H R Q M @ X @ D W Q B Q Q
:LWKRXW \RXU H[DP SOH , ZRXOG Q R R V P E H E W R K W K L Q U G 6 K D Q X I D O V
IRU EHLQJ WKH EHVW EURWKHU D \ W L E W H H Q F R @ B E N D \$ N O W K U R X
P\ \RXQJHU EURWKHU \RX KDYH W D K X J K L W S R H U W B Q P X F H R I D S E B W
ORYH DQG , FRXOG QRW LPDJLQH P U H Q W H V Z E R W H K F D X Q G \ R D X O L F
WKDQN \RX IRU \RX D Q F R D F W F B S W W D Q E S S R Q U P \ 7 F R D B H H U D Q G S D U
DQG :LOPD %ODLGH Z\FW G E F B Q Q R W X W F D R Y U H L B G G P N X V S I S R R X J K
SURFHVV \$OWKRXJK \RX DUH Q R W H K I R O H Z E W K U R H Z Q M R E P I R X O U
OHVVRQV \RX E H O R V Q R Z W G H L Q D R H / B Y H \RX D O Z D \ V

7R P\ VHFRQG IDP L U D \ + B Z O D G 6 D R Q G] O R H X \$ S W K O B I Q N D Q R X I R U D C
7KDQNVJLYLQJV DQG &KULVWPDVHVXIXD O D R O O R Y H W @ B G V X S S
WKDQN \RX IRU EHLQJ WKHUH IRU F G X D V Z I D V F K R R R @ D J R W H G F
XQGHUVWRRG DQG ZHUH VXSSRUW X O H , T P Q J O D R G U W A R K @ D Y , H D P
\RX LQ P\ OLIH ODUJLW WKDQN \RX \ I G H F D O Z I D Q W V X S \$ R L W E
VRPHRQH LQ P\ OLIH WKDW DOZD \ V K D J L Q P H E D F @ D D Q R G \ X Q G R I
DQG \$XUHOLR WKDQN \RX VR P X F K F R H S W L N L Q J Q B H P H D Q C W R O Z
ERWK VXSSRUWLYH DQG SRVLWL Y H W B X X K H G / D L Q R I J U L D G X D K U
ZHUH DOZD \ V W K H U H Z L W K K X J V W P W O H X O D Q B \ R X S S R U W V H L Q H
DV P\ RWKHU KDOI <RX ZHUH W K H U H Q I R O W K R D V G H U R D X Y J K P H Q
HYHQLQJV ZKHQ , I H O W Q R W K L Q J Z D W Z R U N B Q J U D B X D O V G Q R
\RX E \ P \ V L G H 7 K D Q W K H I R Y B O O X B S R I G W O D Q G I Q X B K V Q K X J V

7R DOO WKH ODE PHPEHUV RI WKH A H L L V Q P J D Q J U D H E R W D A X B S R
&KDQGL WKDQN \RX IRU WHDFKLQJ W R I H Q W K H L Q L P S R H U @ D I Q F D Q
IULHQGVKLS 6UHHQL WKDQN \RX FRUUVV I H D Q F K H Q D J Q B H W M R N P @ B
FUDJ \ Y H U \ F K D W W \ X Q G H U J U D G W R \$ S H U R V D I Q G U B X I R U D P S O N
PH ZLWK DQ \ T X H V W L R Q V , P L J K W K P Y H R R D Q G S I W R J Z K D Q N R
(OLVH DQG \$QGUHD IRU WHDFKLQJ I P @ K R Z P W R J Z W H N X D L W R D F
D J R R G I U L H Q G D Q G V R P H R Q H , F R X L O G K B R W W R R X R U W H L P F F W L X R
WRQLFV DQG H P R W L R Q D O V X S S R U W G L V Z R X V G W K L R Y H @ K D R U
JUDWHIXO WR \RX G R W H R K Q L F D S S R Q L G D P P H W K D D F N \RX IRU
VXSSRUW RYHU WKH \H D U V D Q G \ R X E H Z I R U G R W R W H Q V G R P P \ 7 D
XQGHUJUDGXDWHLW X G H Q L W V O B D K U D D O O B R K D Z K H I R H O S D Q G
ODXJKV DORQJ WKH ZD \

/DVW , ZRXOG OLN P \ W D R G D I E W R Q R Z O H O G H V H V X S P S R Q U W R R Y H U W K H
7KDQN \RX IRU DOO H R D W R X H K G I S J D O R E F L A G H I O C R S R Q D W L Y H Z
ORRN L Q J I R U Q R Y @ S Z I R P W L Q R J , H Q S W R F L D W H G D Q @ B B Q G V X S S
WKURXJK WKH 3K ' SURFHVV

&+\$37(5 21(
,QWURGXFWRQ DQG /LWHUDWXUH 5HY

5ROH RI (VWUSURJHGXFWLYH 3K\VLRORJ)

(VWURJHGV ZHUH WKH ILUVW KXP DOV KVDYUREL GWKR D PRRQHSK R
UHSURGXFWLYH IXQFWLRQ (VWUDGLRQK HVRWDLPLDLQQHUV
WLVVXH HVWURJHGV DUH UHTXLUHGHIRHPPDWHV HSPDRGJF
LQFOXGHV WKH RYDULHV IDOORSUDHQXVIEHHVVXWRJHGXV FHQG
IRU ERWK PDWXUDWLRQ DQG IXQFWLRQRJXCEHJHWHOMTXQG
UHJXODWHG SURFHMMGFDFMURRDSHFWMDZDHFQWKSILKSLWDU\
7KH RQVHW RI SXEHUW\ LV LQLWLDW M GUZDFKHG FZKLVFKLQH
SURGXFWLRQ DQGRQHONLVN SHISV LGRUDLQV SHFSWLYDVEHQ VSHI
LQ WKH KISRWKODDPKWWUPBSISWLKSHGHQURQV DOVR H[KLE
DFWLYLW\ WKDW FDXVHV *Q5+ WR ZELFKHOMDMHGHQVLDGXOR
DQWHULRBSIHVXIDWBUWZR KRUPRQHV /+ DQG)6+

/+ DQG)6+ DUH UHTXLUHG VQRDVG LRRORV EBJONDIR QS UERXWIH U
VXEVTXHGW RYXODWLRQ)6+ DWIRGSKILRYKDRLLDRQFHGFXV
DURPDWDVH H[SUHWLVRGQUHDTQGLDFGV LRFVU D+G LRVQLPSWRD
SURGXFWLRQ RI WKKMWRVWHIOGQELQVR YEKUHWRO WFRONGHJV DGM
JUDQXORVD FHOOV ZKHUH LV LVBHRPDRVLD MGDWHR FKHVWB
HVWUDGLRO IURP WKH RYDULHV SURDQGHSLWXHLGWDDFNWVRFR
)6+ VHFUHWLRQ DSWZBODHDDWLRQGXIRPHVGRBPEVDLQGD XPLQD
FHOOV WKDW OLQH WKH XWHULQW LZDDGD XWHV(DGRIPHFUHLDD
WKDW OLQH WKH GXFWV RI WKHOXVQMLDQHR ZDRDODDIGHV LUISJ
JURZWK DQG PDLQWHQDQFH RI D IHVXVHVGXWLDG URSU GJQDQEB
DOVR FULWLFDO IRU WKH GHYHORSPHQQWWRIHWSUR EDIFPDDWWR
FHOOV WKDW QGGGXVWV WRKEXVDSVQDVKPVL DJNH GXQLG WJ BQM JQD

,Q WKH DEVHGFH DWLQEQ WIKWKRUPHS PEGXIFWLDQ B WHUPDFWHV L
7KH IRUPDWLRQ RIRGXGMPHYQWDDUDEM SUPDQFVPRUXHWH RIQVXWH
QRUPDO DQG LV QRW GHSHQGHQWHBQDFWHRSDUWYKHG KHKR(5HV
WKH PDWXUDWLRQSRIRQVKEVXVREUWVWHDGURVHGHFURIMWHVG IURP
WKH (5. NQRFNRXW (5QH WRXVHXWRIDHWVWLDQJ HQGRRIPWU
OXPLQDO JODQGXOODV HESLFRPHVLDORSDQGVWQDIDVXSGEHWQD
DUH SUHVHQW > @ 7KH FHOOV RI(VKPHYGLJLWBDGEHODOXORBSK
DQG WKH IROOHFODVHRHGXDIURMDGDQGHGQRYVNOVKHR UHSURG
UXGLPHQWDU\ DQG WKHUH LV QR RYXIDWLLRQWKH (5.2 IHP

:LWKRXW WKH SUHRDQFHLRIHEDQHSWHLSHGGXFWLRQOLP UHSU
ZHOO 7KH PDOH UHSURGXFWLYH WQREWDLQ WKZH(5H2) PRXV
RI DJH WKH WHVWL VZHLJKW LV ORIZODDQG (5LHPEKDIUDFV
DWURSKLHG VHPLQLIHURXV WXEXLQVG W\SRIZ DSHGJ DGRIFQW
EHKDYLRU > @

7KH (5.2 % (5.2 PLFH KDYH VKRZQ GLISHHWHQMSHGSURGX
ODERUDWRU\ ZKHUH WKH PLFH ZHUH SOBGGXFWQ EHQHWLVVU

PLFH FKDUDFWHULJHG E\ D ORZ ODDW HDUW QMFE B UF BQSD UG SU
OLWWHU PDWHVDW@U\$QRWQGH WKD ERD QHI H P E B H Z HDQG VWHUL

(VWURJHQ DQG ODPDDU\ ODDWXUDWLRQ DQG 'HYH

(VWUDGLRO LV D QRR HDV HPOWED O\ IRO DTQKH PHYPHORS RHO QG
VWDJHV RI GHYHORISHPHDQV SHUHEXURQD O\ S P H W X W D I O D G X I O W
SUHJQDQF\ ODFW DW L R Q D D J H G (H V H U D E G L P H E Q L X O D M S L R Q J W W D I Q H P D W
PDDU\ JODQG GXULQJ WKH SXEHUWHDV >D@G 'X H L X Q D J O W K H P D E
DQG SXEHUWDO SKDVHV RI JODQG GHYHVO R S K P H W Q W P D N O B V X S E
H[WUDFHOOXODU PDWUL[RI WKH P D F P D D O J H O R D Q Q G W W L R Q F G H O
HVWUDGLRO LQ FRPELQDWLRQ ZLWK S S R O L I I H F U D W R Z Q K D I O G F
HSLWKHOLDO FHOOV RI WKH P D P P D P R D J O D I O W S X F W D Q H W W H G H
ILOO XS WKH PDDU\ IDW SDG 'X R J L H Q W S H U R J Q H D O F Q G W S U R R I O R
WKH IRUPDWLRQ RI DOYHRODU O R E X F O W H D V I W R I P H W K W / F D S L F R D G O
PLON > @ :LWKRXW HVWUDGLRO P D V P R D D W L R O D Q Q G V L W H
VLJQLILFDQWO\ LPSDLUH

7KH (5.2 PRXVH L V G F E D X D F W H U G L H Y H O R S H L G / P X D P P S H U R R I G H D Q L Q Q
PDDU\ JODQG DQG HSLWKHOLDO F H O O H E V U D Q R K R Q J 5 L V L G H E
VWURPD DQG WKH HSLWKHOLDO F H O O W K R I U W K L W J O R D Q G D Q Q K
GXFWDO WUHH WRZDUGV WKH P D P P D I U X O R W W S F E G V H U Q H S V L Q P
PLFH ZKLFK VKRZ QRUPDO GXFWDO G S U R I O D W H L Q D J W W R K Q W D W 5
GRPLQDQW UROH LQ PDDU\ JODQGG >X @ W D Q H I H U V P H W M R L O O
LQ UHJXODWLQJ FHOV SUROLIHU R X P L R Q K W H V D D V O W R D E Q F H Q G H I
WR HVWUDGLRO UHVXOWV LQ F H O O W K S D W R O H L I S H U D W W L R Q O L Q (S E U H
H[SUHVVLQR RI (5. S U R G X F H H U B E W V D H Q Q F W Q O S U H V H Q F H R I H V

6LQFH HVWURJHQ V S U W G Q F H S P D Q L R O R W I H F S U R G X Q F W L Y R I Q W L V
RI HVWURJHQ V H F U G W U R Q J W P K H O V S K F X H P R I Q D G V D M Q S E R H S U R G
VWUXFWXUDO FKDQQHM V W K B G G L R O U R M E W K H H O B R Q B H D G W L W K W
KRUPRQDO IHGEDFN ORRS EHWZH HQI O X F W X D D L R O D Q G I W K H
RFFXU LQ ZRPHQ DW PHQRS DXVH ZKLYFKOXDWL R P D W Q I G P O I D Q
+LJK FLUFXODWL Q G Q H Y H G Q R U L E X D Q F U H R D V R Q I R Q H D E S H O V D
ORZ HVWURJHQ OHYHOV OHDG WR X Q F R P D R U K M D V E O B D P H K O H R S
GU\QHVV PRRG VZLQJV DQG VOHHS V G E S M U R P H U Z R P R I Q R K P E Y D H
SUHV F U L E H Q U H R W H B J H L Q W I I H D U V

(VWURJHQ DQG %UDLQ 3K\VLRRJ\

,Q DGGLWLRQ WR LWV UHSURGXFWE S R U H W I D Q F W V S K H W L R O R J H L G
PDQ\ QRQ UHSURGXFWLYH WL V V X H V G L H I G Q E R U D W Q S L V R S Q F W R

UHVSRQVLYH WR IHWWH RUHQXV DWRUHQD V W QFOX GRH N W VMD O GL
WKH IHPDOH DQG PDOH EUDLQ GXUHQDQJ SRUHQDQD S OHGIRYHPDR
DUFXDWH QXFOHXG HGXIDLRQSP S Q WW QDQWQDQW G Q D FLN SRRURV V E
K\SRWKDODPXV DQG SLWXLWDU\ SGRFVHILFQL QD QVKSIDEJWLLFQ
UHJXODWLRQ URD VERIGH WRHQVHRO > @

(YHQ WKRXJK WKH PHFKDQLVP RI DFLVSDRQH LLQXWQKH QVZLQ K W V F
WHP SHUDWXUH UHJXODWLRQ :LWK GRZLDQ GP HQXRSV D X D W L Q R
KDYH KRW IODVKUHW XGDWRRU WKH WUPRQW LRIQH Y W @ R J K E LQ PD
WKHUPDO QHXWUDO JRQH LV XQNQR ZQIRKUR ZR V F B Q Z RUPHSD
WKHUDS\ KDYH UHGXFFRQ KRW D V D Q D QWK DSRH W W D Q R W H D F W R U
SURSHU ERG\ WKHUPRUKH XGDWQ Q D Q Q D Q K H S W K M V F U H J X O D
RI WKH K\SRWKDODPXV EUDLQ EKKH LPD M R X Q F I G H D W Z K L F I K H
RQ KRW IODM K V I T H V W X D W H R Q Z L W K P R X V H Q H X U R Q V V X J J H V W
+RZHYHU RWKHU VWXGLHV KDYH VKRZ Q R W K D Q D W K H V (5 . Q D D R U
> @ & O L Q L F D O O \ Z R P H Q W D N L Q W H) V W U R V I K I R Z D D B Q I U H
TXDQWLW\ DQG VHYHULW\ RI KRWWHO D V K I H W E R W K (7 5 K H D V H G V (3
LQYROYHG LQ WKHUPRUHQDQWLRQ LDQ GP B R W W I D D W K I F S W H P Y
HTXLOLEULXP QRW RQO\ LQ WKH W D H L P S H E J D W X D O H V R R Q W F U R I O R
WKH HTXLOLEULXP R G R F W K L Y H Q R L Q W X H I D V Q G X D I G I D S V R W I K H V E V V X H
LQIODPPDWRU\ PHFKDQLVPV

\$QWL LQIODPPDWRUQ 5RQWKH VWRUHQDQHG \$GLSRVH 7L

Estrogen and the Bone

(VWURJHQV DUH LPSRUWDQW LQ PDIQQWBLW LQJ P B Q H I P Q I O H
IDFWRUV WKDW SURPRWH ERQH UHFRQW S J M P R Q H) R L L Q K H L D O L V P K S
SURFHVV RI ERQH UHPRGHOLQJ UHQW LFUHQVO W W K S H D F W W L K H W E R
RVWHRFODVWV DQGWK E I O D R Q W I R U V F L L O R V W D V F L G F Z K D F K E U H
H[WUDFHOOXODUODW D I Q O R I Z E Q Q R V D H R G R Z D V W H Z H O R Q H W 7 K
DFWLYLW\ RI RVWHRFODVWV WRPRV Q W B E Q D Q W W X F I H L F Q V H Q L W
GHQVLW\ > @ (VWUDGLRO LV LP S R I U D V D Q L W L L Q \ F E D I W Q Z H I D I Q Q W
W\SHV E\ UHJXODWLQJ JHQHV DQG > D S R S Q V D Q L G / S R U R V P R W I R Q J
EXLOGLQJ DFWLYLW\ RI WKH RVWHRFODVWV FPHQGH Q W S H O R , Z
HVVURJHQ OHYHOV VWLPXODWH E R W D Q J L Q I R O D Q P I D Q F L R Q D V E
F\WRNLQHV LQFOXG) L Q Q G / ,) 1 , / D O W U R I E Z K W I F K W R R D F W L Y D W L F
FHOO DFWLYLW S W L R Q E R Q H U H V R U I Q Q F W W R Q D G W R L Q F U H D V
7*) IURP RVWHREODVW FHOOV GHG H M S R Q Q L E W K H I R D F W L H Y
F\WRNLQHV V X F K % D V G H I F U H D V L Q J F Q V D R N L Q H F V O I G U D F W L L R Y D W L F
HVVUDGLRO KDV D SURWHFWLYH W R O L H Q E O D L P K L W L W Q Q J E R Q

\$OWKRXXJK WKH PHFKDQLVPV RI (5. D Q G G H U V W R R I G H E W Q L W D
(5. LV UHVSRQVLEOH IRU WKH SURHDFH V 5 L Y H D H S E B W D Q R R S S
LQ ERQH IRUPDWLRQ E\ UHSUHVVLQJ P D . O D F W L Q E Q Q J 5 V . B Q F G H

IHPRUDO ERQHV DV ZHOO DV DQ DQFUFHDFVH>LQ E@QHZ KHHUWRD
KDYH LQFUHDVHGL FDKQ FENQCHV V) XU VFWUWVDR B XW B D QWH(5.ZGHYH C
RVWHRSRURBRLWWPH@RSDXVDO ZRPHQ ZLWK ORZ DOHYH DQV R
LQFUHDVHG ULVN RI RVWHRSRURVDFWGLXHWWRDQQ EQ@UWHDNV
GHFUHDVH RI ERQH PLQHUDO GHQ VHLVH LQ LSR Z WPHIQ RASDNXLVQ
IRU KRUPRQH UHSODFHPHQW WKH@HDSLD YKHG UH YMKW DQW VL V
HIIHFWV RI (5.

Estrogen and Adipose Tissue

(VWURJHQ V DQWL LQIODPPDWRUX HIEH FSWR DROW RQR F@XSRDQ
R[LGDWLRQ DQG GHFUHDVLQJ ERWKRFDWHVWSRURDG XFBQ@ YD
F\WRNLQHV DQG DYHL SSRNLQCH ODPKDW KUFARDFWULLYELXWH ZKWR RE
PHWDEROLF V\QGURPH ,Q RYDULHFDWRLQJ HGV W B B JHQV OPHYGH
LQFUHDVH LQ JRQDGDO DQG YLVFHUD@FRD@MLSRQV LWG HFRPS
HVVURJHQV UROH LQ DGLSRVH UHJRXCH WQ RQV V@R@OWKRXJ
IXOO\ XQGHUVWRRG LW LV NQRZQWWRQ WLGH VWUROH QDQCFU
OLSRJHQHV LV LQ DGLSRVH WLVVHM WPRVIFQV DRQGWKLY F XV7@
E\ WKH XS UHJXODWLRQ QRU3B\$H VZ XKHOFDS BFRMLGRJH IDW >
PLFH SKHQRW\SLFDOO\ KDYH LQFUHDVHG GDWUDXQFXDQX D@W SRQ
JRQDGDO DQG YL@RQDQZLW B HIGB@V@LWQF@H.2VHLGH KDYH
JOXFRVH WROHUDQFH DQG LQVXOLQ WHSUMWHDQWHZ@W@ D@
SKHQRW\SH VXJJHVWLQJ WKDW (5.VPH@GL@SRVHHVWV@RXHQ
HVVURJHQ PHGLDWWRGDIJH UH@WZLHDQGYXIEVFXWDDH B@VSRVH
LQFUHDVLQJ . \$ DGUHQHUJLF UHFH@SWRUL VYXUHVXLV@R@V
:RPHQ DW PHQRSDXVHVH K@L@HE@R@K@DF@L@R@P@L@Q@D@D@B@X@P@X@D@V@H@L@R@
DVVRFLDWHG ZLWK DQ LQFUHDVHG W@D@E@R@D@L@F@V@H@Q@L@R@P@S@L@Q@Q@G@
ZLWK HVVURJHQ UHSODFHPHQW

OHFKDQLVP RI (VWURJHQ \$FWLRQ

(VWURJHQ SOD\V D SURPLQH QW UROH ERWKKH HPSDJRQXHF@D@Q
UHSURGXFWLYH VHSO@XFFHP@D@ML@Q@W@V@V@Q@B@S@D@K@V@H@L@Q@S@B@U@Q@W@L@V@
GHFUHDVH WKH QGVWRRL@FLVHHDVHH W@K@H@Z@R@B@Q@W@V@R@V@U@R@L@J@H@Q@L@
UHSODFHPHQW WKHUDS\ ZRUNV WR GRFFL@W@D@H@G@Z@L@W@S@W@R@P@Q@R@
+RZHYHU HVVURJHQV LQ PHQRSDXV@D@L@R@R@V@P@R@G@H@W@I@K@H@E@V@S@
PDNHV LW LPSRUWDQW IRU GHYH@R@R@S@H@Q@M@R@U@H@5@D@I@B@B@R@V@H@C@
VHOHFWLYH HVVURJHQV WKH PHFK@Q@E@M@P@X@Q@G@H@U@W@W@R@R@G@Q@7@
FKDUDFWHULJHG PRGH RI DFWLRQ@R@W@U@H@V@Q@M@F@R@U@L@S@Q@W@L@R@Q@L@E@X@W@D@
VRPH ELRORJLFD@L@D@W@I@H@G@W@W@K@D@B@X@J@K@H@Q@R@Q@J@H@Q@R@P@L@F@S@D@W@K@Z@D

Nuclear Estrogen Receptors ER and ER

(VWURJHQ DFWLRQ LV PHGLDWHG E\%HRWVKU BUIRQ WULHGFV SWRIU
VHSDUDWH JHQHV IRXQG RQ GLIIHUHQCEWGFHGU BPRVKRPH (65 > JHG
RQ KXPdq FKURPRVRPH ZKHUHDV (5 VRPHQFRGHG(E) (Z
GLVFRYHUHG DQG FKDUDFWHULJHGOLQDQD\ UGZRHGFKIGVR
HVWURJHQ ELQGHGJISRP WKLHQ ULWR XDWUUXNL L> @E 7KH H
RI D VFRQG HVWURJHQ 5ELZG LQQRSQVGMV FRYHEU HX VW DIVVR
%RWK HVWURJHQ UHFHSWRUV DUH PHUHPHLOV RIK W KX KXHF DU
VXSHUIDPLO\ LQFOXGHV SURWHLQV ZKLFHKS DWRH MLJDDQGF DE
ZKLFK UHJXODW S WJLROHEW UDFQVLEODPDDG KIRJXODWRU\ HOHPH
7KH IXOO OHQJWK (5. DQG (5 UHFHSWRUVHG BRQKWLRODD DLGQ
) 'RPDLQ \$ % IRXQG WZLWKLQX WKFR GLDQGHSHQGH OWJDQV
IXQFWLRQ LPSRVLFDDWHLQHQRDJKGRWDRQ LTKLV \$RPRJHQ
LV WKH OHDVW FRQZHUGHGKGRPHLQGLRU VG RPKDLQ \$ VEL FRO
DQG LV LPSRUWDQW IRU SURWHLQ FRSQVLDLQUD FGLPHQLYDRWL
D OLJDQG ELQGLQJ GRFDLQZKHGK DSHQGHQW DQWIGYDWRQ
\$) 7KH \$) VHTXHGFH LV LPSRQWDFRWFIRUYDMRUX SWRQJH
IRU JHQH UHJXODWLRQ > @

ER . and Activation of Genes

(5. DQG (5 DUH QXFZKLFK UXHFHSWRQWEDQVFLSDQRQDO UH
ELQGLQJ WR VHTXERWVSRPHLEWUMKORXDFWIKJLHQJELQGL
SURWHLQV %RWK (5. DQG FRQWDLQDUFRW, HJLDQFGIEQJH
FRRUGLQDWHG ZLWK F\WHLQH PROJLFXOHMLQJHU@ RDP
VSHFLILFLW\ FRQWDFR WZKWKDWDQDFHQWUHFQVSRQHG ZLWKL
RU HQKDQFHU VHTXHGFHV RI UHJXODWRWKG HMQHDQ VFSU/LSUHLR
7KH HVWURJHQ UHFHSWRU FDQ ELQGHPRQW XQZLWSQLQ KKRHPB
HVWURJHQ UHVSRRMWHQMPXGQWGLFVLQGHILQFKVLRQVLRWV RI D
SDOLQGURPLF VHTXHGFH ZLWK D WKUSHR QXF@HRDQGHQSH
ZLWKLQ WKH JHQRPB FRQWDLQ DQ QD\ RQHDKDDU LQDQW (5Q
ZLWK GLIIHUHQWLDQ QXFOHRWLGHOMSBELQVQ ZHWZDSU LPHORJX
ZLWKLQ WKH SURPRWHU UHJLRQV URW KIRJXQDQW BBTXHQDFV QBX
LW ZDV IRXQG WKDQWVKUHHGRFRWQDQGLDQDFHJXODWRU\ UHJ
> @ :KHQ (5 ELQDQVFRMUR UHQ IHRQV LWKLVFWGR R RDKWLQVWDXHQ
WR PDNH FRQWDFW ZLWK WUDQVFRUSMLRQDQDQDFKJLQDQW
LQGXFH RU HQKSDQERQWRIDQKRVRH JHQHV
(5 DOVR FDQ LQWUHJXODWZRWKFRWHPWRW\$HEFLMLFWSKURWELQV
WR SURWHLQV ZKLFK GLUHFWO\ EULQGXORWHSWHUHQPHFQW\$W(L
GRQRWFRQWDLQDQ (5(ZLWKRXW KHDYILQW KVRJHG BWHHFWDQFU
FRPSOH[LW\ RI HVWURJHQ UHFHSWRUHQJXQDQWQIGWRUUGDQVFR
ZLWK SURWHLQV)RS/ -XQ. L\$QWHDQDFMVZLQDKOWK\$BLQGLQJG
6S DOORZLQJ LW WR EHFRPH WHWOKDWHG JHQMVKHLQSFURXPRLVQ

ZKLFK LV D JHQH (S)SUROL
,W KDV EHHQ VKR
WR HVWUDGLRO DD
SURWHLQ H[SUHVVLQR
SURPRWHUV 'XH WR D KLJKO\ GLV
RQ HVWURJHQ

(5 DOVR WHWKHUV WR \$3
(5 LQWHUDFW ZLW
SURPRWHUV RI UHJXODWHG JHQHV
SUROLIHUWLRQ
VSHFLILF ,Q ERWK EUHDVW FDQFHU
HOHPHQWV ZKHQ E
WDPR[LIHQ EXW QRW ZKHQ ERXQG
JHQH LQ WKH SUHVHQFH RI ERWK
IXQFWLRQDO DFWLYLW\ RI OLJDQGH
GLIIHUHQW FHOOXODU UHVSQRVHV > @

Coactivator Recruitment

(VWURJHQ UHFHSW RUH JXODWLRQ
UHJXODWRU\ HOHPHQW GLIE
PDFKLQHU\ ZKLFK LV ERWK OLJDQ
GRPDLQ RI WKH HVWURJHQ UHFHSW
FKDQJH H[SRVHV WKH
ELQGLQJ DQG DOOR
LV D URWDWLRQ LQ KHOL[+ ZKD
RQ ZKHWKHU WKHRU
ELQGLQJ SRFNHWOW
WUDQVFULSWLRQ IDFWRU SURWHLQ
/;;// PRWLI LV SUHVHQW LQ D
WKDW LQWHUDFWV ZLWK WKH /%'

7KH S IDPLO\ RI FRDFWLYDWRU
65& DUH DPSOLILHG LQ EUHDVW
PHWDVWDVLV > @ 65&V IXQFW
&RDFWLYDWRU SURWHLQV UHFRJQL]H
LQWHUDFWLRQ FRDFWLYDWRU
FKURPDWLQ UHPRGHOLQJ FRPSOH
ZKLFK UHGXFHV
7KLV FDXVHV KLVWR
WUDQVFULSWLRQ IDFWRU UHFUXL
SURPRWHUV RI UFWLX
WUDQVFULSWLRQ H
WKH\ DOVR ELQG ZLWK FRUHSUHV
H[SUHVVLQR RI F

ELQGLQJ RI WKH FRUHSUHVVRU LV ERWK DOVR (5 L W \$ & H V F U X K W V K
&RUHSUHVVRU FRQWDLQ D / ; ; , + , L W , W R K I H O W H P B F W I Z W W
(5 2 Q F H W K H F R U H S U H V V R U L V E R X V G O D V R H (5 L W \$ & H V F U X K W V K
DFHW\O JURXSU IURP KLVWRQH V O H \$ G S L Q H Y M R M I Q Q D W K H G I Z U
WKH EDVDO WUDQVFULSWLRQDO P B F K I D Q H I U U H D Q X G O W H E U X L Q V W
RI WKH WDUJHW JHQH

ER . and Repression of Inflammatory Genes

2QH XQDSSUHFLDWHG DFWLRQ RI H V H W U H F J M Q V \$ L Q X P E H I U R D
LQFOXGLQJ RVWHF S X O D R V G L V H F D V I G L B V P K V R L P H H U L W \ G L Q G D W U
ZKLFK RFFXU GXULQJ PHQRSDXVH K D S Y R Q B I Q W P \$ R J W M D Q W U L Q K
RI WKH PROHFXODU PHFKDQLVPV Z K L R U C H E R X I O B U R J D H Q W B Q K
IRU LQIODPPDWRU\ GLVHDVHV , Q O F R I Q W L U D W I Q R V Z R J H E R X W F W
ZKHUHE\ HVWURJHQV UHSUHV V J H Q H V H Q K M E H S I V M U L R H Q V
VWXGLHG WKH PRVW (VWURJHQV U H S) U H E X V U H G L O X D P L Q W R (5 \
OLNH RU 1) % HOHPHQWV 2QFH WKH W K W R X W K I W K U D Q H G F U L S V
UHFUXLWV WKH FRDFWLYDWRU Z W L F K K H F D I Q V X Q F W L R Q K I D U H D
SRWHQW DW DFWLYDWLQJ WDUJHW B Q Q W H K S R Q U W S H U D V H Q H
SURLQIODPPDWRU\ JHQH V

Non-Genomic ER Functions

(5V DOVR KDYH W R B X F E L Q R W \ J W R R S P L F Q H I U H F S W G E H O D X V L J C
FURVVWDON ZLWK JURZWK IDFWRU V L E R X Q I G Q H V F D V R D H Q W
(VWURJHQ UHFHSWRUV FDQ DFWLYDWH W K H S K R V S S K R U S O D M
H[WUDFHOOXODU VLJQDO UHJXODWRIGS K R Q D O D W H D (5 G > Z K L
UHJXODWH WKH H[SUHVVLQR RI J H Q L R V L Q Q R O Y H U G L L Y O F H O K
LQFOXGH F\FOLQ' >> @ D Q G K H O V F L Q F H W F R I Q W S H S R L U G H W K H L
HVWURJHQ UHFHSWRU LV ERWK D V H H T S U R W W H L L Q H G 6 W Q G L B Q
WUXQFDWHG IRUPV RI (5. V X F K D O X Q S D U P B P E I U D I Q X W D M O H H G S
WR DVVRFLDWH ZLWK SURWHLQV V P E F U D Q M E R Q Q B R Q L V Q D U H
DFWLYDWH WKH O \$ G . H V I R J Q B B O O J J E U R V W K R D Q G . L Q D W K I H V S H F X
EH LPSRUWDQW L Q D V Q P R D P S R J R I J U Q W H D V R W W D Q F H U L Q E

7KH SKRVSKRU\ODWLRQ RI (5. LV D O V B Q L P S U R L S W D Q W D I R U D F W
SKRVSKRU\ODWLRQ RI VHULQH R I 5 (5 . L Q G U H H F W H X L W W W
FRDFWLYDWRUV (5. D Q G (5 ERWK I E Q Q G \ H K W Z H Y G L R O H Z L F V K
UHJXODWHV L W V 5 R Z O W E W H R I W K H Q Z O W R W K H L Q S R O H Y J X O D W L
IRU SUROLIHUWLRQ D Q G F H O O U X U Y L Y H D Q H Q S H V G B Q G B B I Q X I O
ZLWK (5. E O R F N L Q J L W K H W D H J X O D W H I R Q D M I L R Q W H V R E Z W K D W
KDYH GLVWLQFW I X Q F O L R R U \ D P H F K I D I Q H V B V > @

Current HRT and the Two-Ligand, Two-Receptor Mechanism

7KH HIIHFWV RI HVWURJHQ DQG SURJHVWHURQH ELQGV WR WKH SURJHVWHURQH ELQGV WR WKH HVWURJHQV LQ WKH XWHULQH WLVVXHV @HS:RPFHQW HQDM L GHFUHDVH WKHLU ULVN RI GHYHORSLOQW DXMHQWL QH WFDUHQFHQ D PDLQWDLQLQJ VKRUW DQG ORQJ WHSHQWFKHQJKL WVK IR IF R R E E Q E KDV EHQHILWV SURJHVWHURQH KDV RIJHVFWHU RQH LWHVHRS FRPELQDWLRQ RI RHMWVWHURQH DQG DGS UEVRI DDQV LQDFWHDU/ HL QF FDUGLRYDVFXODU GLVHDVH > @

7KH ZRPHQV KHDOVK:ELWLDWHLHEORQG SRDEER VWXG\ WKH ULVNV DQG EHQHILWV RI KRUEVQKDWHSDFDXVHQW DWKH LQ KLS IUDFWXUHV EXW DQ LQFUHDH %RWEKMDKHWL QEQEB HQGRPHWULDO DQG EUHDVW FDQFHU XLODVLRFBD SHBOZLWU LQ ERWK WLVVXH 7KH FRQFOXVLRQRUPWH WKHZDDSWKDF EHQHILWV \$IWHU WKHVH ILQGLQJVQRUIRRQYKWKWUDBU VX PHQRSDXVDO DQG YDJLQDO V\PSWRERQ%PHFDXWHRVKIRUWLW IRU SUHYHQWLQJ RVWHRSRURLV ZXILUKW QRQQ WRHUPLDE WKHUDS\ WKHUHVWUDVHGHFRUHS LWEVURHIVHOHFWLGHDO WUHDWLQJ PHQRSDXVDO V\PSWRPVZHXORZEMHUQHDZQHFWR WKH HIIHFWV RIHQBRJLQRXODHWMDRWVQPSWRPQWWRKVDU KR YDJLQDO GUIQHVOJ ZKLFOSRULHWLHYHQHIIZLFWKR RQ IADKXVHQVHC ULVN RI EUHDVW RU HQGRPHWULDO FDQFHU

Tissue-Selective Estrogen Complexes for HRT

:LWK WKH QHHG WR GHYHORSVVDHMOHQDFWHRUWKHUFRVPEUQDW QRYHO DQG FODVVSORQV(QQ6WQCHHH(5FEEEDWYIS SLLR/SHU PRUH WLVVXH VHOHFWLYH HVWURHQQRPEQOMKHVINQRZQ DM 2EVHUYDWLRQDO VWFQGLH5X6/LQDPRQDQHQ RDIYHDVQRZQ WK GHFUHDVH WKH ULQSRMWIRHQRVSDXWD ONZRP HQFWRZMMHKURW YHQRXV WKURPERHPEROLF HYHQWV HQQGH LQKMKULVNDVRH RQ FDQFHU > @ %HFDXVH RI WKH506LGH HQILFFDVOV D WKRFLDW GUXJV WR XVH IRUDVHPSWQPPHQRSQDQVQRWUQD5050 %DJH %=(KDYH VKRZQ WKDW LW LV SRVWLEJHWWRUDVQB PDMHF 8SFRPLQJ FOLQLFDV%H(VBDBKQXDLQWVHURWDLVQERJHQV E\ GHFUHDVLQJ ERQH WXUQRYHU DQBXWHHQFGHHDVHDLQHS FDQFHU ULVN > @ \$OWKRXJK %n=vtro&DQVLQKRZLQSEIBL WKL 76(& VWLOZRUHQX LHJRVHQRXQJKHVWURJHQSRDQGEV\ LC UHSURGXFWLYH FQFHUFIXQDWEQJ)DLWVWRWHQWQXIGYLIHQVRQ WR RI %=(DQG UHSURGXFWLYH FDQFHUQDLWINRDXDQVBLGRQHDV VHULRXV EORRG BRMDUFBQGXWWRVWVORIEEGQBPSRQGVZ DV LQGXFLEOH HVWURJHQ UHFHSWRXODRVRXQDDVORRQH(ZLWDR HIIHFWV RI ORZREJLQFXQDWKRXVWVWVQBHGVRWRHJISQRXIV HVV FDVHV ZKHUH HQGRJHQRXV HVWURBHQVVDHFRQG VFRIPISRLXHQGV

LQVWLWXWHG WR ORZHU WKH GRVHURHIGMFRDHQWVXHVWUHR
HVWURJHQV ,Q WKERXZDG ELGBPSRXVSGVZLPWQVDQDQHRWURJHC
WZR OLJDQG RQH UHFHRSXWDWRDQFKDQHLWRI LPDVLQV DQWV R J H Q
LQFUHDVLQJ WKH VLGH HIIHFWV RHHFHZEKVQLWRH 3RZRHQWJDD
VXFK XQLTXH HVWURJHQBHOSLQDQFVRVSRGQV KSKYHQHVIHQHXGLFL

ER . Coagonists for Future HRT and a TowLigand, One-Receptor Mechanism

)RU FHQWXULHV ZRPHQ KDYH XVHG QHDWRWWRQDQV 8PKLQF
V\PSWRPV 3ODQWV DQG KHUEV FRQVLIQFQFQGLQDVLVROQ
FRPSRXQGV DQG GHULYDWLYHV VXFKEDQGFQDQFBEWVYZWHF
ODQ\LVRIODYDQRLGV DQG FKDOFRQHLFIRPSRXQGFVRDQW (BL
DQWLSURDLFWWVWVYFW@YH5FRVHSCRXQVGMXPDYREHGHYHORSLO
WUHDW KRW IODVKHV EXW LW LKH XSCROILNVLOYHWHKDHFWWVKHRQZ
REHVLW\VLQFH VWXGLHV LQGLFDWLBWVHGHVH (5HQ%ILFVFDQ
FRPSRXQGV LVRODWHG IURP SODQWVZKWFREDELEHGSDQV/IDFOWL
FRDJRQLVWV ZKLFK FRXOG FDXVHJH5QHWRWVHDMXQFVWEGDFGLL
HIIHFWV

%DVHG RQ FOLQLFDO VWXGLHV WKFDQ[ISVVRIGQJHDJRHQLLVXW
WKDW OLPLW WKHLU WKHUDSHXWVFIXVHZR8XIQUMQWVDNHK
FRQWLQRRXVHFWWURJHQRV QHGXFHDLQWHDQSRGBDEWZHLJKV
SRWHQWLDQVWUDWHJLHV IRU QYHQVWHURJHGVKVDSDH EIHUQV
D6(50 VXFK DV ED]YGR[LWVQW UHRZLPHLQRLQODS/SKURRYWHGVHUP
WUHDWPHQWRIKRWVHFRDQVQVQDQVULRDMWVHFRVURPSWLVRQDQG
DGYHUVHVLGH HIIHFWV VXFK DV YHQRRRQVQKURPEREPIERQV
KDYH GHYHORSHG ZKLFK DUH YHU\ SUHPLDQVQHEBFVXRQ
8QIRUWXQDWHODWLVKMXQZILQGEVWHKISRQVLYVIRHJJKWJDL
EHFDXVH (5. LV WKH PDMRU UHFH\$WRKULUQSRQVLEBQGLDGLS
FRPSRXQGV WKDW DFW DV (5. FRDJRQLVWVVELTCKGLVQJFRFRS
VLPXOWDQHRXVO\ZLWKHVWUDGLRQWKQVZKLGMLRBUHQV5.OZL
FRXOG DOWHURVUKHSEFRVHJLXQV MQVDMVDFWVJLDDQVHFVHQLR
DOWHULQJWKHSEVWHGUQRHJH.QHFRVDRSLVWVKFRSKOGLRORJ\
WR SURGXFH GLIHFUHQW7FGLLQFFRQSVHRIHVVRJBJRQLVWF XQL
VFUHHQLQJPHWKRGVZLOOKDYH VPHVHRXGLORLJHGVV&ORDVH
VFUHHQLQJFRPSRQVQVWRUEVQGLVFRDSEKRIUHVQGRJHQXEH (5
UHSRUWHU DVVD\ &RPSRXQGV WKRVXJKLQ5G DMRHDFQGDVFW
HVWURJHQLFZKLFKDDUPHXSREAHFDVRLQDQSUHFSQIRIGXEDWLYHWL
FODVVLFDQVFUHHQLQJWHFKQLTXHXVPHDQVURRYHQV DQSO8
FRDJRQLVWV PD\JR XQGLVFRYHUH (5.EBEBXRHWHQVQRWHSXV
FOLQLFDO HIIHFWV 7KH NH\ WR IQQVQLV DQRHLVGHURVHIO DHP
FKDQJHV WKH WUHQVFBLSWVLRQDOLVWVHDSRQVHQWRKHV GL
GHPRQVWUDWHWKDW ¶ ¶ ¶ WRIDKVRQLR[VWZ&DFIRQHJIKWDE
SUHYHQWLQJDQGDWVRBMDLVQHGGZLVWVPHVQRSDXVH

5 () (5 (1 & (6

6FKZHQN (DQG) +LOGHEUDQGW S1JDXUZLVVHQVFKD
:LOOLDPV : 3 , , , 6 -DUMLVLDQH CCG cadah CNHhOY HQ / -
Kisspeptin and a Gated GnRH Response Mediate the Preovulatory Luteinizing Hormone
Surge. (QGRFULQRORJ\ SJ
.DQJ + : \$QGHUVRM Modulation of Reproductive Morphology and Growth by
Estradiol-17 and an Estrogen Antagonist- RXUQDO RI & HOO \$JLRORJ\
/XEDKQ ' % - 6 ORGHQJ 7-6) *RRXVH2 .6P LARKdBFK
of Reproductive Function but not Prenatal Sexual Development after Insertional
Disruption of the Mouse Estrogen Receptor Gene 3URFHHGLQJV RI WKH 1DWL
RI 6FLHQFH 8 6 \$SJ
.UHJH - - % +RGJLQ -) &RXVH 0DKOPDUN 0DUDUQ
.RUDFK - *XVWDIV Generation and Reproductive Phenotypes of Mice
Lacking Estrogen Receptor 3URFHHGLQJV RI WKH 1DWLRQDO \$FDG
SJ ±
\$QWDO 0 & \$.UXVW 3Steady State Absence of Histopathological
Defects in Non-Reproductive Organs of a ERbeta-null Mutant 3URFHHGLQJV RI
1DWLRQDOV \$FDGHP\ RI 6FLHQSHV 8 6 \$
6LPLDQ 0 < +LUDL 0 1DYUH = The Interplay of Matrix Metalloproteinases,
Morphogens and Growth Factors is Necessary for Branching of Mammary
Epithelial Cells 'HYHORSPHQWSJ
*UDKDP - ' & Physiological Action of Progesterone in Target Tissues
(QGRFULQRORJ\ 5HSJLHZ ±
%ULVNHQ & . 6DDDEMDHW %LQXW5 5:H6XWKHUOB .H
& 2UP Polactin Controls Mammary Gland Development via Direct and Indirect
Mechanisms 'HYHORSPHQWDO %LRSJ\
1DIWROLQ) . - 5\DQ , - ' The Formation and Metabolism of Estrogens
in Brain Tissues \$GYDQFHV LQ %LRSJLHQFH
\$UDL < \$ Synapse Formation of the Hypothalamic Arcuate Nucleus during
Post-Natal Development in the Female Rat and its Modulation by Neonatal
Estrogen Treatment 3V\FKRQHURHQGRFSJLQRORJ\
.DOUD 6 3 Neural Regulation of Luteinizing Hormone Secretion in the Rat
(QGRFULQRORJ\ 5HSJLHZ
/XLQH 9 1 6 7 5LFKDUGV Estradiol Enhances Learning and Memory
in a Spatial Memory Task and Effects Levels of Monoaminergic Neurotransmitters
+RUPRQHVDQG %HSDYLRU
6LPSNLQV - : 3 6 *UHHQ . (*ULGH\ * 056RDNKPD &
of Estrogen Replacement Therapy Memory Enhancement and the Prevention of
Neuronal Loss Associated with Alzheimer's Disease \$PHULFDQ -RXUQDO RI 0HG
SJ 6 6
'HHFKHU ' & Understanding the Pathophysiology of Vasomotor Symptoms
(Hot Flashes and Night Sweats) that Occur in Perimenopause, Menopause, and

Postmenopause Life Stages\$ UFKLYHV RI :RPHQ↑V 0HQW\$0 +HDOWK

%URFNMRaging Menopausal Symptoms: Hot Flashes and Night SweatsXUVLQJ

6WDQGDUG SJ

=DQJ / % (%ODFNPDQ 0 ' 6FKRQ;HBDQQ 07 7DRORDLHF

+ \$ +DUULV , &RKHQ 5 \$ 3HUD 6 +HLWEDQ 5 , :

Receptor Beta-Selective Agonists Stimulate Calcium Oscillations in Human and Mouse

Embryonic Stem Cell-Derived Neurons3XEOLF /LEUDU\ RI 6FLHQFH 2QH

+DUULV + \$ - \$.DW]HQHOHQE Characterization of the DW]HQH

Biological Roles of the Estrogen Receptor, ERalpha and ERbeta, in Estrogen Target

Tissues In Vivo Through the use of an ERalpha-Selective LigandGGRFULQRORJ\

SJ

6WRYDOO ' : - MF-101, an Estrogen Receptor Beta Agonist for the

Treatment of Vasomotor Symptoms Peri-and Postmenopausal Women&XUUHQW 2SLQL

LQ , QYHVWLJDWLRQDOSJUXJV

6LPV 1 \$ 7 Coupling the Activities of Bone Remodeling and Resorption: A

Multitude of Signals within the Basic Multicellular Unit %RQH. (\ 5HSRUW

*DUFLD \$ - & 7RP 0 *XHPHV * 3HQDQFR\$ 00(LUDDGD

&DURERQL 6ER. Signaling Regulates MMP3 Expression to Induce FasL

Cleavage and Osteoclast ApoptosisRXUQDO RI %RQH DQG 0LQHUDO 5H

SJ

&KHQ) < 2X\DQJ 7 < H Estrogen1 Inhibits RANKL-Induced

Osteoclastic Differentiation by Increasing the Expression of TRPV5 ChannelRXUQDO RI

&HOO %LRFKHPLVW\$U

%DNHU 3CD4(+)T Cells and the Proinflammatory Cytokines Gamma Interferon

and Interleukin-6 Contribute to Alveolar Bone Loss in Mice.RXUQDO RI ,QIH

,PPXQRORJ\ SJ ±

:HLW]PDQQ 0 1 6 &HQFL / 5LI Interleukin-7 Signaling 5 3D

Osteoclast Formation by Up-Regulating the T- Cell Production of Soluble

Osteoclastogenic Cytokines%ORRG SJ ±

:HLW]PDQQ 0 1 & 5RJJLD * 7RUDO 6 Increased HLW]PD

Production of IL-7 Uncouples Bone Formation from Bone Resorption During Estrogen

Deficiency -RXUQD 0DPI ,QYHVWLJDWLRQDOSJUXJV ±

&HQFL Estrogen Deficiency Induces Bone Loss by Enhancing T-Cell Production

of TNF-. -RXUQDO RI &OLQLFDO ,QYHVWLJDWLRQ

&HQFL Estrogen Deficiency Induces Bone Loss by Increasing T Cell Proliferation

and Lifespan through IFN-gamma-Induced Class II TransactivatorURFHGGLQJV RI

1DWLRQDO \$FDGHP\ RI 6FLHQFH 8 & \$

*DR < Estrogen Prevents Bone Loss through Transforming Growth Factor Beta

Signaling in T cells 3URFHGGLQJV RI WKH 1DWLRQDO \$FDGHP\ R

SJ ±

+XJKHV ' Estrogen Promotes Apoptosis of the Osteoclasts Mediated by TGF-

beta 1DWXUH 0HGLFSLQH ±

. RUDFK . 6 0 7 DNI The Effects of Estrogen Receptor Gene Disruption
on Bone : RPHQ↑V + HDOWK DQG 0\$1QRSDXVH
3DQ / & + = .H + \$ 6LPPRQV ' 7 L&QNDZ6R3JG0F&XU&K
- 5 6FKDIHU . 6 .LPEUR 0 7DNL .Estrogen Receptor ' ' 7KR
Knockout (ERKO) Mice Lose Trabecular and Cortical Bone Following Ovariectomy
-RXUQDO RI %RQH 0LQHUB 0 5HVHDUFK
*UXPEDFK 0 0 5Estrogen Receptor Consequences and Implications of Human
Mutations in Synthesis and Action7KH -RXUQDO RI (QGRFULQRORJ\ DQ
SJV

5RJHUV 1 + - : 3HUILHOG . - 6MOE Reduced Energy 2ELQ
Expenditure and Increased Inflammation at Early Events in the Development of
Ovariectomy-induced Obesity (QGRFULQRORJSJ ±
' (RQ 7 0 6 & 6RXJD 0 \$URQRY\$V] *U6HEQ540J6 .)U
Regulation of Adiposity and Fuel Partitioning. Evidence of Genomic and Non-genomic
Regulation of Lipogenic and Oxidative Pathways RXUQDO RI %LR,ORJLFDQ &K
: S.J

+HLQH 3 \$ - \$ 7D\ORU * \$,ZDPRW Increased Adipose EDKQ 3
Tissue in Male and Female Estrogen Receptor Knockout Mice 3URFHHLGLQJV IURF
1DWLRQDO \$FDGHP\ RI 6F5HQFH
3HGHUVHQ 6 % . .ULVWHQVHQ 3 \$HQH%PD5LQKHQ\$V
Estrogen Controls Lipolysis by Up-regulating Alpha2A-adrenergic Receptors Directly in
Human Adipose Tissue Through the Estrogen Receptor Alpha. Implications for the Female
Fat Distribution -RXUQDO RI &QRORJFDQ QGRFWIDSRJOLVP

37. (QPDUN (0 3HOWR +XLNNR . *UDHQQDLVHQ 6* 5/DJKILMVF
& - +DUULVRQ Localization of the Estrogen Receptor Locus (ESR) to
Chromosome 6q25.1 by FISH and a Simple Post-FISH Banding Technique
SJ ±

38. /DJHUFUDQW] - *)ULHG 0 1 Human Estrogen Receptor- \$ * X
Beta Gene Structure, Chromosomal Localization, Expression Pattern RXUQDO RI &OLC
(QGRFULQRORJ\ DQG 0HSWDEROLVP

39. -HQVHQ On the Mechanism of Estrogen Action3HUVSHFWLYHV LQ %L
0HGLFLQH SJ ±
7RIW ' DQGA Receptor Molecule for Estrogens: Isolation from the Rat Uterus
and Preliminary Characterization3URFHHLGLQJ RI WKH 1DWLRQDO \$FDQ
\$ SJ ±

.XLSHU * * ((QPDUN 0 3HOWR DKLVRNOR of a Novel DVVRQ
Receptor Expressed in Rat Prostate and Ovary3URFHHLGLQJV RI WKH 1DWLRQ
6FLHQFH 8 6 \$ SJ ±
.XPDU 9 6 *UHHQ * 6WDFN 0 %Functional Domains of Q 3 &
the Human Estrogen Receptor&HOO SJ
.KRUDVDQLJDGHK 6Nuclear-Receptor Interactions on DNA-Response
Elements 7UHQGV LQ %LRFKHPLFDQ 6FLHQFHV
&ODHVHVVHQV) DNA Recognition by Nuclear Receptors(VVD\ V LQ
%LRFKHPLVWU\ 1XFOHDU 5HFH\$SWRU 6XSHUIDPLO\

%XUFK - % 0 (YDQV 7 0) Two Functional Estrogen Response Elements are Located Upstream of the Major Chicken Vitellogenin Gene &HOO %LRORJ\ SJ
&DUUROO - 6 RQJ 0H\HU 7- 56 *H(LVFNKLRQJMH \$ 6 %UR
(. .HHWRQ . &)HUWXFN *) +DOO6HPH:DOFKKQYRHN(L
)R[3 \$ 6LOYHU 7 5 *LQJH Gene-Wide Analysis of Estrogen Receptor Binding Sites 1DWXUH *HQHWLFSJ
%RXUGHDX 9 - 'HVFkrQHv 5 0pWLY%UHWVFkIDHIDGH
*DQQRQ - :KLW Gene-Wide Identification of High-Affinity Estrogen Response Elements in Human and Mouse ROHFxODU (QGRFULQRORJ\

3UDOO 2 % 6DUFHYLF (\$ 0XVJU Erogen-Induced Activation of Cdk4 and Cdk2 during G1-S Progression is Accompanied by Increased Cyclin D1 Expression and Decreased Cyclin-Independent Kinase Inhibitor Association with Cyclin E-Cdk2 7KH -RXUQDO RI %LRORJLFD &KHPLVWU\
6DIH 6 . \ Non-Classical Genomic ER/Sp and ER/AP-1 Signaling Pathways -RXUQDO RI 0ROHFxODU (QGRFULQRORJ\
%UJRJRZVNL \$ 0 \$ 3LNH = 'DXWHUQ 5VWURPEEDU 26PD
* / *UHHQH DI\$VRXQVW Molecular Basis of Agonism and Antagonism in the Oestrogen Receptor 1DWXUH SJ
&RZOH\ 6 0 6 RVDHUP DQ 0 Estrogen Receptors Alpha and Beta Form Heterodimers on DNA -RXUQDO RI %LRORJLFDOSJ&KHPLVWU\
\$QJLFN 6DAUBKSHWDR Receptor Coactivator Amplified in Breast and Ovarian Cancer 6FLHQFH SJ
:DOVK & \$ / 4LQ - & 7LH The Function of Steroid Receptor Coactivator-1 in Normal Tissues and Cancer, QWHUQDWLRQDO -RXUQDO RI
SJ

6DYNXU 5 6 The Coactivator ULL Nuclear Receptor Recognition Motif -RXUQDO RI 3HSWLGHSHVHDUFK
.DUPDN 6 (\$)RUWH Roles of p160 Coactivators for Regulation of Breast Cancer Cell Proliferation and Estrogen Receptor alpha Transcriptional Activity (QGRFULQRORJ\ SJ
.HOO\ 0 - (Rapid Activation of Plasma Membrane Estrogen Receptors 7UHQGVLQ (QGRFULQRORJ\ DQG SHWDEROLVP
/DQQLJD Estrogen Receptor Phosphorylation 6WHURLGV SJ
'XELN ' 7 & 'HPELQ Stimulations of c-Myc Oncogene Expression Associated with Estrogen-Induced Proliferation of Human Breast Cancer Cells &DQFHU 5HVHDUFK SJ
'XELN ' DQG Transcriptional Regulation of c-Myc Oncogene Expression by Estrogen in Hormone Responsive Human Breast Cancer Cells &KHPLVWU\ SJ
&KDXGKUL 5 \$ 1 6FKZDUW] . (OEDD GfER-36in 6FKZDUW Membrane-Associated Signaling by Estrogen WHURLGV SJ

62. \$FFRQFLD) 3 \$VFHQJL \$ %RFHGHQWDCSLVCH 3 9IR
0DULR Mitoylation-Dependent Estrogen Receptor Alpha Membrane Localization:
Regulation by 17beta-Estradiol ROHF XODU %LRORJ\ RI VSKH & HOO
3DSSDV 7 & % *DPH Membrane Estrogen Receptors Identified by
Multiple Antibody Labeling and Impeded-Ligand Binding. KH -RXUQDO RI WKH)H
RI \$PHULFDQ 6(RSHHWPHHQWRO %ISRORJ ±
.XLSHU * * % &DUOVVRQ . *UDQG LHQ1LOV (RQD UN \$
*XVWDICOMPSON of the Ligand Binding Specificity and Transcript Tissue
Distribution of Estrogen Receptors Alpha and Beta QGRFULQRORJSJ ±

1RUWK \$PHULFDQ 0HTOR 2012 Hormone Therapy Position Statement of
the North American Menopause Society 0HQRSDXVH SJ ±
=KX / : & %URZ Estrogen & Treatment of Ovariectomy Protects Against
Fatty Liver and May Improve Pathways Selective Insulin Resistance' LDEHWHV
SJ ±

0DNL Critical Window Hypothesis of Hormone Therapy and Cognition: a Scientific
Update on Clinical Studies 0HQRSDXVH SJ ±
\$QGHUVRQ * / + / -XGG \$ 0 .DXQRWQ '0+3%VWWDQJHUS
6 * 0F1HHOH\ Effects of Estrogen plus Raloxifene on Gynecologic Cancers
and Associated Diagnostic Procedures: The Women's Health Initiative Randomized Trial."

7KH -RXUQDO RI QWKHG \$PDL\$VVRFLDQLRQ
*DQQ 3 + 0 Combined Hormone Therapy and Breast Cancer a Single-Edged
Sword 7KH -RXUQDO OF BQ WKBLSFHOU \$VVRFLDQLRQ
*DPEDFFL Selective Estrogen Modulators in Menopause LQHUYD *LQHFROR
SJ

5XQRZLF] & ' - 3 &RVWDQWLQR ' /: 0LFRUHQLOP /5*6
)RUG 9 * 9RJHO Gynecologic Conditions in the Participants in the NSABP
Breast Cancer Prevention Study Tamoxifen and Raloxifene (STAR) \$PHULFDQ -RXUC
RI 2EVWHWULFV DQG * \QHJRORJ\

0LUNLQ 6 Management of Osteoporosis and Menopausal Symptoms: Focus
on Bazedoxifene/Conjugated Estrogen Combination QWHUQRWLODQI -:RPHQ
+HDOWK SJ

0RRUH Advances in Menopausal Therapy: the Tissue-Selective Estrogen Complex
-RXUQDO RI \$PHULFDQ \$XUWHBDVWELWSRQHUV
:XWWNH : + -DUU\ 6 :HVWSKDQHXWPHHQWRIHO
for Hormone Replacement Therapy? RXUQDO WHRLG %LRFKHPLVWU\ DC
%LRORJ\ SJ ±

/HFOHUFT * Interactions of Flavones and Other Plant Derived Estrogens
with Estrogen Receptors for Prevention and Treatment of Breast Cancer-Considerations
Concerning Related Efficacy and Safety RXUQDO RI 6WHURLG %LRFKHPL
%LRORJ\ SJ

&+\$37(5 7:2

0DWHULDOV DQG 0HWKRGV

&RPSRXQGV

&RPSRXQGV ¶ ¶ K Q W B Q K \ G 7 U R [\ F D Q G G U R ¶ \ F R D W F R Q H 7
REWDLQHG IURP , 1'0) &1R P S K O R L F + D O O V P S R X Q G V Z H U H & V R W R U
URRP WHP SHUDW XURP DQLG KSW R V R W F W M G B V P D F G O X E A L B Q W V Z O Y L G
FRPSRXQGV LQ (72+S \$XOOG R VZKHUWH FRREPW \$ DCGHG FIKU R 6W6 L/JFPXLV

3UHSDUDWLRQ RI 6WDEOH &HOO /LQHV

+XPDQ RVWHRVDUFSRPHDV FHOJ DO MQHWG B(F\F OBL QH (5 H J X Q G W(5
8 26 (5 F'1\$ ZHUH SUHSDUHG FKDU DSFWWHY U R J X M G O \ D G G V P W D L
&HOOV ZHUH PDLQWDLQHG LQ '0(0) H G \ X I S I S V O D H P H E R W H I G H Z
*HPLQL %LR 3URGXFVV 8 P/ RI S H J Q R / F I L X O D J L Q R Q Q H G D V M G U H
JOXWDPLQH \$OO FHOOV ZHUH FRQWLLQX R X V G O L D P V X S S V O D L P Q H O
—J P/ RI K \ J U B R \ G L Q % J P/ RI J H R F L Q

%UHDVW &DQFHU &HOO /LQH 0DLQWHQDQFH

0&) EUHDVW FDQFHU FHOO OLQHV ZHUHDL QREOV DLQQ HQG 0IURP
VXSSOHPHQWHG ZLWK IHWDO ERYLQH R H B X F S H Q L F I L O L O % G
VWUHSWRP \ F L Q J P/ I X Q J L J R Q H D Q B F R Q W L X V X B R V Q H P \$ Q
SKHQRO UHG IUHH PHGLD

7UDQVIHFWRQ DQG /XFLIHUVDH \$VVDIV

JV RI D SODVPLG FRQWDLQLQJ WKHP(5G LXS V W U Q I D V H R O X F
SURPRWHU DQG JV HLWKHU &09 (5. RVUR & 0 2 6 5 F H Z O V H F W D W D O
E \ H O H F W U R S R U D W L R Q > @ & H O O R X Z M U M K W Q H O W H G D R Q G D
OXFLIHUVDH DFWLYLW \ D F F R U G L Q J R W H R J W K H R U P S Q X I D G F W X R U C H U
WKH /XPDW /%* %HU(WKROG 7HFKQRORJLH%) :L D G E O G Z H U P I
WUDQVIHFWHGWZL V K F W K H U D S (H S O D V P L G

&RPSHWLWLYH (VWURJHQ 5HFHSWRU %LQGLQJ \$VV

8 26 (5. DQG (5 &HOOV

8 26 (5. RU 8 26 (5 O V W D J E O R Z Q H L Q Z H U O H D W H V G K H R U Z H U K R X U V
DQG ZLWKRXW —J F O J G A R K H F V F O H Q W L P Q S H O W E D W H H G O V Z H U H K @ Z
>+ @ H V W U D G L B F O W \ V S M F L I L & L P P R C F L H Q U F N I L Q % B P W R Q L I H \$ @
SUHVHGFH RI L Q M U B D V L R Q J F R R Q ¶ H Q ¶ ¶ ¶ 7 7 & & \$ R W H U Z D V K L Q J
ERYLQH VHUXP DOEX(P72Q ZQ V 2 6 G H Z H I Q G U R H H O W W K H Q W
DIWHU KRXU 6SHF@ I H F V E U Q G L R O R D X H F D L O I F X O H Q V H I G E B W Z H H
QRQVSHFLILF ELQG ISHU L R L Q X O V H F R X Q L Q V ' 6 \$ K / H T : D L O G B F L Q W L O
&RXQWHU

0&) &HOOV

0&) FHOOV ZHUH J U L R Z Q V L Q Q S Z H H O O O O) U H G / X I S S O H P (H Q W H G Z
V W U L S S H G) % I 6 L Q F H X O E D W Z H G U > f & + @ K @ W Z L D V G K L R O O >> V S H F L I L
& L P P R O 3 H U N E Q H Q P H U % R I V W 6 R Q H Q D F S H @ R I Q L Q W K U H S D V H Q J
F R Q F H Q W U D W L R Q V \$ R W H U Z P V H L Q + J & Z L W H K U X P D E O R E Y L R L Q L Q 3 %
(7 2 + Z D V D G G H G D Q G H Q H V O K N Q Z M U K H Z S G F L I W F I U E L O G R L X Q U R I >
H V W U D G L R O Z D V F I D I O F X I O O F W H G H D V Z V S H E F W R F V E O Q D Q L Q J R Q & 3
S H U P L Q X W H X V L Q J 6 \$ V K I H T X D G O 6 F F L Q W I H O O D W L R Q & R X Q

51\$ ([WUDFWLRQ DQG 4XDQWLWDWLYH 5HDO 7LPH 3&5
7RWDO 51\$ ZDV H[WUDFWHG DQG WKXQ XAPU HIRWWHGO ZLWSK 0L
%LR 5DG /DERUDWRULHV +HUFXOFWL&QV ZHVHUS/HUWRUDDQV
L6FULSW F'1\$ 6\QWKJVRUWRWDLZLWKS%IDF5RGG\$QRWRRRO 4X
3&5 ZDV SHUIRUPHSGZLWY;K D7KHLURPDO &X7DQJU 6XRYDHPV (YD
6XSHUPL[%LR 5DG 0HDQ " 6(0 ZDV FIDVWXQDVSHURJXVDFQJ*3
6RIWZDUH ,QF 6DQ 'LHJR &\$

0LFURDUUD\ DQG 'DWD \$QDO\VLV
7RWDO FHOOXODU 51\$ ZDV LVRODWRHGG NLWL 0% LIRQ5 DVGKH \$XEX
SHU WKH PDQXIDFWXUHU V GLUHFWWRIRQMG 5E1\$ QDQRDWRHS/
TXDOLWDWLYHO\ HYDOXDWHG E\ VPIDQ XIDF V DGH(PSVILQR/QV V X
ODEHOHG F51\$ VDP SOHV ZHUH SUHS LURHG Q VLDGEJHOHQ JV BPS
HYDOXDWHG E\ ERWK DEVRUE DQDHU \VSGHFWWBB&RWRHPV
F51\$ VDP SOHV ZHUH K\EULGLJHG RYHUQLJKW D'HDQ&WL\$X
DUUD\V \$I\PHWUL[6DQWD &ODUDLQ&\$UL\$SOOL FDUWHD VQ&QW
RI PLFURDUUD\V ZHUH XVHG IRU DOOXWHG DWRP BQWIR U&OW K W
FOXVWHULQJ EDVHG RQ 3HDUVRQ XRWUHO DRMLBQQFRH ZILW
H[SUHVVLQR SDWWHV W&MQ7XVHGG LHWZ YDMKD OQJGH SWKRG&OH WK

&KURPDWLQ ,PPXQRSUHFLSLWDWLRQ &K,3
&HOOV ZHUH SODWHG DW FRQIQXIKQFJ DQGRMFFHFDWLQGH MR
UHFHSWRU H[SUHVVLQR IROORZHG Q\O VHUWVUVDVDFHLQW ZLWKT F
7+& RU WKH FRPELQDWLRQ RI HVWG DGLRXU DQGHQOVJ ZHPH +
; IRUPDOGHK\GH VROXWLRQ IRU Q PLQX W K I V Q D F W H G U I D Q G
ZLWK 0 JO\FLQH VROXWLRQ &HOOV XZSHUHH ZIDQWHHG ZILWKK
LQKLELWRU FRFNWDXVLRQ F&G'ILV QFRSROHLFW HGG \$LQD Q&OOHF
P0 7ULV +&/ S+ DQGVXB&SOHPHQWHGQZILW KWSUR WRHFNVM
FHQWULIXJHG DW USP PLQXWHVQD WK WU D3HO OOUH W&H ZIDU
WKDZHG RQ LFH DQG P/ RI O\VLV EXIIDH&O P0 7ULV S+P0
(*7\$ 7ULWRQ ; WIDQGH;LSUKRELWRGJH&F N&WHDLOO OZDDWH
GRZQ DW UFI PLQXWHV DW UUDGG VQ&BQS M&SHUWQ DDDO

LQ P/ 5,3\$ EXIIHU P0 7ULV S+ P00 11D& Q & P0 ('7\$
7ULWRQ ; 6'6 LQ&URWWRDUV 0R7 NZWIDHVRQDLF\$ WHG IR
VHFRQGV RQ DQG VHFRQGV RII 6 DPSSFO HRUZH UHL QXWGI VO
DQG VXSHUQDWDQW ZDV FROOHFWWHLR Q6 ER SIGHV ZHUH UGLWOK
1D '2& P0 7ULV DQG P0 1D& Q HDZQGV WBNHHD FRUW
DQG VWRUHG DW Û 6DP SOHV ZH QWV VSRG WZIDQWDRG GHGR XSDV
URWDWHG RYHUQLFRKPSOM[HÛ ZHPN 0FRJQDHWLVF HGH \$KDQRVH E
+HDOWKFDUH 3LWVWVDEKXHG KL Q3 \$, 3\$T X/OZHU H& RR OOHFWHG RY
RI WR KRXUV URWMDWR QS ODHVH ÛV KHU P 0FR OMI FV BBDGV ZH
WLP HV DQG WKH '1\$ LZOW ZOWWHG XWHRQ VRODW&RQDW Û
(OXWHG '1\$ ZDV FOHDQHG DQG FRQFHQDQV &RQ FXVQV WDWKR
5HVHDFK ,UYLQH &\$ \$QWL (5. DQWHERG\ V& DZHU K
SXUFKDVHG IURP 6DKQRD &UX]6%QRM5 &UXPE&\$ \$QV&2\$6 ZDV
SXUFKDVHG IURP \$EFDP %XUOLQJDPH &\$

:HVWHUQ %ORW

8 26 (5. FHOOV ZHUH SODWHG DW DGRQV LVMORIGLVKHV HDOO
KRXUV ZLWK J / GR[\F\FOLQH &HOODVQZHUHK WXUHQ ZLVWK
(72+ Q0 HVWUDGLRO 0 ¶ ¶ ¶ ¶+ & ¶RU ¶W74& DRQGE HQDW
&HOOV ZHUH ZDVKHG ZLWK ; 3%6 DQXIMFU B B Q W DRQQ LQH LQP
13 1D '2& 6'6 P0 7ULV S+QG ; PSURW \$ DDV H
LQKLELWRU FRFNVEDMQRGRF, QIG L'DQVSLD VWHBQ\$ EORRVV LG
SKRVSKRU\ODWHG DQWDERGLQKLED WSKR QSKGN WDWLODZDV FR
5RFKH 'LVWULEXWLRQ ,QGLDQDSIRQH G BWS &HSE CRVDW
DW Û 6XSHUQDWDQW ZDV FROOHFXWHLQ JD W G HW 9 2D5\$ 'SQRDU
DIWHU VWDLQLQR PSURWHLQOZXVW KDRW B MQ \$KMDPR 6FLH
5RFNIRUG ,/ 3URWHLQ O\VDWH VDPSC H 0DZP SOH P\XHG UZID
5HGXFLQJ DJHQW DQG UXQ XVLQJ W XIQ, QLYQ JW 2 RJIHQ W XSVSOP
ZLWK 1XSDJH DQWLR[LGDQW 39') PHP EURDQ HD QZG VS UDFWHLVQ
WUDQVIHUUHG LQ 1XSDJH WUDQVIH, V QDXQIGU1 < LIVX \$B BKQRIQ
PHWKDQRO 0HPEUDQHV ZHUH VRDNKMG DW SÛLIRDORDB
VHFRQGDU\ IRU KRXU DW URRP WHE]SHG XWIXQH WKHP E&D\$
:HVWHUQ %ORWWLQJ 'HWHFWLRQ 5HBR BQM V \$RHHGVKOP OXGH
VF 6DQWD &UX]6%QRM5 &UX]P%LRWHFKQRORJ\ Q5D VSKG VSKRLQH IURP
/DERUDWRULHV %/P 6DQWDF WUQ]I%RRWHFK QRFRQJGDVIF DQWL
LQFOXGH DQWL UHDEE L W J, QD G 5 Q J & HFQSQ RQFQJUR%MYBIQV PR
+53 FRQM XJDWHG G DQFWD &UX]P%LRWHFKQRORJ\

3RLQW 0XWDWLRQ &RQVWUXFWV RI (5. /%'

\$OO FRQVWUXFWV ZHUH REWDLQHG IURP QW-KCHO OH L&QPLDYQH UV
&DOLIRUQLD %HUNHOH\ (65 SRLQW R & MDDQVHR G V WZH UH H
0XWDJHQHVLV .LW 6WUDWDJHQH &D -R8050 \$U R \$ X EDQ G SV H F SD
D &09 YHFWRU

&HOO 3UROLIHU DWLRQ 6WXGLHV

,QKLELWLRQ RI HVWUDGLOROD SLQFGXVFIHHGVDWGLREQ SZDDVWLQJ
ZHOO RI D ZHOO WLVVXH FXOWXUH VGLS/SKOHQ HSKW E B CZ UMG I
IHWDO ERYLQH VHUXP *HPLQL %LR SLQFGG XFWUHSWRB\PLQRI
IXQJLJRQH DQG PO JOXWDPLQH &HFBQVZHBH WZHDVQDGHIVR
SOXV DQG PLQXV LQFUHDVLRQJ GRGHV-RD ¶H¶OV¶ZH¶H DOV
ZLWK HDFK GRVH RI ¶ ¶ ¶ 7+& DORQHPR&H¶OV¶HWHH DRXG
QXPEHU ZDV FRPSDSDGWLRLQXWERO RQUGDWRWR[ERQMU

&HOO &\FOH \$QDO\VLV XVLQJ)ORZ &\WRPHWU\

0&) FHOOV ZHUH SODWHG DW D GRQVZMOOR IWLVVXHFH¶OW
SKHQRO UHG IUHH '0(0) VXSSOHPERQYLQGH ZLWKP &WOC
WUHDWHG IRU KRXUV ZLWK FRQWURO ¶72¶ 7+¶OS¶XWDDG
HVWUDGLRO &HOOV ZHUH ZDVKHG ZILQKHUR ZPWKHPLS\$VDQX
VSXQ GRZQ DW USP IRU PLQXWVKHOFHGQO ZBOCHVSLUC
ZDVKHG RQFRQGWK 3%HGRZQV\$%G ZHG BMSHDDKVDPSOH SH
/ RI J O 3URSLGLXP LRGLGH VQXWDDG ZBVWDQGHGLWF
PLQXWHV 6DPSOHV ZHUH UXQ RQ BZ)&\WRPHWU\ &¶QWRH
/6\$ 8& %HUNHOH\ &\$ DQG GDWD ZDV DQDO\JHG XVLQJ)ORZ

ORXVH 3XUFKDVH +RXVLQJ DQG 0DLQWHQDQFH

0LFH RQ D VR\ IUHH FKRZ GLHW

ZHHN ROG & %/ - IHPDOH RYDULHFWRPP E DFG VRLQ H DZERUHDV
6DFUDPHQR &\$ 0LFH ZHUH KRXVHG\$DQVPOGQWGLSQRG HDG
WKH 1\$) IDFLOLW\ DW 8& %HUNHOHHH&\$K\$DGLPHLWH ZHUH +E
/DERUDWRULHV VVWUHPROJH RQ\$ ZHHN EHIRUH RVPRWLF SX
ZHLJKHG RQFH D ZWHLRQRRI WKKH GXSJHULPHQW

ORXVH RVPRWLF SXPS SUHSDUDWLRQ DQG LPSODQDWLRQ

0LQL 2VPRWLF 3XPSV ORGHO ZHUH OSXG FZLDWKH GHIKIRPO \$
HVWUDGLRO PJRI ¶ ¶ ¶ 7+& ¶7+¶WIKG RHPVLUQDGLRQ \$QO
PDGH XVLQJ D ODPLQDU IORZ KRIRGFBQGLQWLQRIHIG L'Q6ZV
(72+ DQG ', ZDWHU 3XPSV ZHUH KQDGOHGHZLWKLQWHDUL
ILOOLQJ WXEHDQG P/ V\ULQJH \$QO SPXPSWHZLLOH FQDHFQO
LQFXEDWHG RYHUQLJKW DW Û 3XPSV ZHHN HRQXUJL%DO-OIH
RYDULHFWRPLJHG PLFH -DFNVRQ /DLERU DWRWKH6DFD\$XQDWD
GXUDWLRQ RI ZHHNV

'HWHUPLQDWLRQ RI 0RXVH 7LVVXH DQG %RG\ :HLJKW
7KH PDPPDU\ JODQGV ZHUH GLVVHFVHLY VDXHD DQGR ZHW KKH
LQWUDSHUDWRQHUP R R Q G G D G I Z M W X M Q Z H W G F R O X H G V G W D L Q
DQG JRQDGO IDW WULPPHG SULRU WR R H Z H X U H G J L O R X V D P V
ZHHN

51\$ ([WUDFWLRQ DQG H Z O D Q W H W B & W L R Y H \$ Q L P D O 7LVVXH V
7LVVXH V ZHUH GLV D W F W O H G U B R Q H G L E O H G H T R I U G H 5 1 \$ U L R R H D W L
ZHUH KRPRJHQL]HG LQ 3XUH=2/ XVLQJRQ K W 0 3 R) D D V O 3 5 U \$ S Z
H[WUDFWHG DQG WKHQ WUHDWHG ZLW L Q L 1 \$ L W H I R V L Q D W W K H D \$
7LVVXH %LR 5DG /DERUDWRULHV L R Q F X E B F W & \$ Q V 5 B H H V
XVLQJ WKH L6FULSW F'1\$ 6\QWKHVRUWG ILQJ ZV R U R D U Q V I R S E U R R W R D
T3&5 ZDV SHUIRUP 5 H G Z &) W K D K H U R D O & X F O H U 6 6 A R) D H P V (Y D
6XSHUPL[%LR 5DG 0HDQ " 6(0 ZDV FIDV W X Q D V S H G J X V D P Q J * 3
6RIWZDUH ,QF 6DQ 'LHJR &\$

8WHULQH 7LVVXH 6OLGH 3UHSDUDWLRQ
8WHULQH WLVVXHWZLVP UHG R Y H G F D Q G L D G L X S R V Z H W H V M X H G L G
IRU KRXUV WKHQ WUDQVIHUUH G WR (7272HR UR D Q R K R X H U I F
\$IWHU IL[DWLRQ WLR V X N W E S I D W K R H O R W D V I R I U H U H O H F H X D H V &
WKH\ ZHUH SDUDIILQ HPEHGGHG V H O F L V L B Q G G H B Q G Q V I R D L P R H U
H[DPLQDWLRQ

5 () (5 (1 & (6

7 H H 0 . , 5 R J D W D N L V &) R V W H J D U \$ 5 & Y R U R U L - V W \$ Q . 5
< D P D P R W R ' & E s t r a d i o l & S e l e c t i v e E s t r o g e n R e c e p t o r M o d u l a t o r s
D i f f e r e n t i a l l y R e g u l a t e T a r g e t G e n e s w i t h E s t r o g e n R e c e p t o r s A l p h a a n d B e t a R O H F X O D U
% L R O R J \ R I W K H & H S J O
7] D J D U D N L V) R V W H J D U & \$ 5 / R * P I O L H] L W S P E G & R e p r e s e n t s
h u m a n T - c e l l L e u k e m i a V i r u s T y p e 1 T a x A c t i o n o f T u m o r N e c r o s i s F a c t o r - A l p h a G e n e
T r a n s c r i p t i o n - R X U Q D O R I % L R O R J L F D O & S J H P L V W U \

&+\$37(5 7+5((
5HVXOWV

UHVSHFWLYHO\ 7KHLV VQDWD GJHPF QWVVEBWB ELQSG VDQG (5 Z
VLPLODU DIILQLWPX FEK VRLZV LG IDV BLODRV MRKIDIDH KWUH FHSWR

¶ ¶ ¶ 7+& EHKDYHV DV D XQLTXH EQDJBZQLFWORQV JHQH
7R GHWHUPLQH LI ¶ ¶ ¶ 7+& EHKDQH BQDVR JDI QFRXWJ RQH
UHJXODWLRQ ZH H[DPLQHG WKH H[SULHYVW UHQHRI.5NQR ZDQ
1.* (DQ HVWURJHQ DQG 6(50 UHJXODWV (5G B HQB V) ZHXUHWU
IRU KRXUV ZLWK HVWUDGLRO LVQDFRPEILHQD WUWUD D BGLIMQ
3&5 ZDV GRQH (VWUDGLRQH HQHQ) SXUHSVGRQ KHUHDV ¶ ¶
GLG QRW LQGXFH KHQRPIESLQHWMLRQZSOXV ¶ VWUDGLRO V\
.57 WR IROG

7DPR[LIHQ DQG UDORJIXIDWHG L57 QRQVQKHU[SDVH WMLR\ EORF
HVWUDGLRO LQGXFH BQH SZLHWV WRLKH FBQZDHOXO DFJROULFWWHD FWI
7DPR[LIHQ DQW LYDDWRHIGI HQ*H(DH[SUDHQVLRQI FEOG)LJXU
\$ % (VWUDGLRO DFWLYDWHG 1F*W(ZEDV RIRVOGU YZKH ZHW
¶ 7+& 7KH FRPELQDWLRQ RI ¶ ¶ L]HG74&* SOX[SHHWULBQ
IROG ,Q FRQWUDVW WR WKH VQQH UJLWVSHUHVDFMLRQVDP
RU UDOR[LIHQH KDG DQ DQWDJRQVWWRQIMRW E\ DQGHUHDV
¶ ¶ 7+& LQ FRPELQDWLRQ ZLWK WQRIE LWHQUD QIGI HFDV FGLG
IROG FKDQJH WR DQG IROG 7KHDIORRPIELQHDZLWRQ RI V\
SOXV HVWUDGLROJEVORENHIGQVKEHQV BHFVLRQVRI ¶.* ¶ 7+&
HVWUDGLRO DORQH 7KH GDWD GHYFRQDW UDDW QMTWIK DFRD ¶
HQGRJHQRXV JHQH VWUJXODWLRQ QRG HQRVWL G XFGH J

7R GHWHUPLQH KRZ ORQJ LW WDNHW RRLQ GXF ¶ JHQ7+ & \SOXU
FHOOV ZHUH WUHDWUHGTZLVK ¶ HVWUDGLRODHWLRQQRBU
KRXUV)LJXUH 7KH PD[LPDO V\QHUJLZDVRRE57U YJHQ BWH[
\$W WKLW WLPH BEXFWGHDWUDIGORZOLSBFJHSDZKHHLQHDV ¶ ¶
7+& KDG QR HIIHFV 7KH FRPELQDWLRQ DEWLYDRVHG .5LJXU
\$ 7KH V\QHUJ\ EHWZHHQ HVWUDGLRZDDQRE VHU ¶ HGTWV
DQG)LJXUH % PD[LPDO JHQH V\QHUJLZDVVRXG\HWV KGH
WKDW WKH PD[LPDO V\QHUJ\ IRU WKDW57 K DQG 1.* (JHQH

7R GHWHUPLQH LI ¶ ¶ ¶ 7+& EHKDRYQHGHQVH DQRW KWW DQGLD
DQG 1.* (PLFURDUUD\ DQDO\VLV ZDVI B BQH KZR XWKV 8E D6.HGH
WLPH FRXUVH GDWD)LJXUH ZLWK ¶ Q& HDVORUDHG LRLD
FRPELQDWLRQ &HOOV ZHUH WUHDWVHQ ZEWKUBODWLK EJKVR
EDVHG RII RI WKH ,& YDOXHV GHWLQU PLXUHG V\LV K8 26R FF
)LJXUH \$W GVKHV, DWD D R W QH GURDWLUB QD NFRU IWR RFFX
ZLWK WKH VLPXOWDQHRXV ELQGLRQJ(BJ ¶ (VWUDGLRQ DQGX
WRWDO RI JHQVWZKH BWHIGVZEMCK WVKH ¶ FRPEZEWDSVLRQHV
UHJXODWHG JHQDORQH ZHD ¶ W-RBWDQORDWHGHQHV)LJX

7KUH FODVVHV RI UHJXODWHG JHQDWHV, HUHSHGHMFRPWW KGH
UHJXODWHG E\ HVDWUDDGLRQLDQGRQHW DQDWPFHQW& 7KHUH ZH

UHJXODWHG DQG GRZQ UHJXODWHG & JH QHV , UHJXODWHG
DQG SRWHQWLDWHG E\ WKH DGGLWLRQ RI XSTUH XG & W
GRZQ UHJXODWHG JHQHV & ODVV ,, UHSUHVHQWHG JHQH
HVWUDGLRO FRPELQDWRQ 7KHVH UHJXODWHG JHQH FRQVLESHU
UHJXODWRQ ZDV REVHUYHG ZLWKZ(V RYHQHV ZHUH ZF&WD
QHZ JHQHV UHSUHVHVG E\ WKH FRPELQDWRQ ZIDIEFKH Z
XQLTXHO\ UHJXODWRQHE\ HVZKULFGLRUEH WKJXODWHG LRO D
7+& SOXV HVWUDGLRO UHJXODWHGREQ WKH FRPELQDWRQ +
HVWUDGLRO)LJXUH

7KUHH RI WKH KLJKHVW UHJXODWHG KFHQDMLF D, WJHVQH VZHFU
E\ 573&5) *5H) LJX \$. & JXUHL % 5 DQGHQHV) LJXUH
& ZHUH QRW UHJXODWHG E\ HVWUDGLRO DOR+&HHVXWD
FRPELQDWRQ

& ODVV ,, DQG ,, JHQH UHJXODWRQ LV (5. GHSHQGHQW
7R GHWHUPLQH LI WKH UHJXODWHG RWRHGFDV/ . , 8 DQG FHOJ
WUHDWHG IRU RDXUW ZLWK HVWUDGLRO RQHQRWLRQ LQ WK
SUHVHGFH RI WKH (5. DQWJRQLVW W, & ODVV3 & 5 JHQH V. L5
) LJXUH \$ DQGH* () L% ZHUHQGHJXODWHG E\ HVWUDGL
DQG V\QHUJLJHG E\ DGGLWLRQ RI UHVSHTFVH & HVOR\ DQGH
RU , & , WUHDWPHQW DORQH GLG QRWHVQGXKFDHGHQLW HRSU RI
7+& SOXV HVWUDGLRO GELORF MHUQ KVK. H 7L QGDG WLRQ (R HQ
& ODVV ,, JHQHV . L56) LJXUH QRWDQHJ* GDWHG 'EZH
7+& RU , & , WUHDWPHQW DORQH ZLWK HVWUDGLRO
. L56 DQG) *5 JHQH H[SUHVVRQ E\ KH DQGHLYDWRQ , & , ECK
DQG) *5 JHQHV GHPRQVWUDWLQJ WKD, WJHVWUHJXODWHG
(5.

7+& DQG PEVLDG RQ HQK DQFIH V5. UHJXODWHG HQW
SURWHLQ WR WKH .57 SURPRWHU

\$ PRGHO IRU WKH SRVLEOH V\QHJUSVMVLRQWLQDFWDRQ
7+& SOXV HVWUDGLRO LV UHJXODWHG LRO FKHDXQLHP RI
V\QHJ\ WKH DPRXQW RI (5. DQG 65&57 SURSWREQWHUFZXL
GHWHUPLQH E\ & HQDQDWHG WFRUKRW RKRXWUDGLRO
(5. ZDV UHFUXLWHG WR WKH .57 SURPRWHU & ES OXVRHGW
WUHDWPHQW LQGXFHG D IROG UHFUXLWPHQW RSI V5. PRGE
K) LJXUH 7+& VGHQK DQGHFHUJXWV DORQRI 65 & D
EXW UHFUXLWPHQW RZDORXQFUHDWRQ MI & DQKEERWR HVWUDC
7+&) LJXUH 7+& DORQH GHGWRWREQWFRI HLW
65 & DW DQ\ WLPH SRLQW

¶ ¶ ¶ 7+& SOXV HVWUDGLRO WUHD(5 P S I O R W R L Q D Q G F L W O V O
SKRVSKRU\ODWLRQ VWDWH

2QH SRVVLEOH H[SOFDQDWHBQ(5RIDVQGH6& LUHFUKXDW WKH
7+& HVWUDGLRO FRPELQDWLRQ HQKIDQFHLQJ(5WKSUSWRVLSKRV
VWDWH ZHVWHUQ EORW DQDO\VLV DVQW RSWDB& 5DZBXQFVRQ
(VWUDGLRO LQFUHDVHLC OVRWHDQ (5WMSRUKRRXQWFURFOS D H H G V D
SKRVSKRU\ODWLRQ RI (5. DW VHULQMFULSWKRRQ OOH D G F W W L
¶ ¶ 7+& GLG QRW FKDQJH RYHUD\OL(5G XSFUR SIKIRLQSQRVHO
(5. DW KRXU 7RWDO DQG SKRVSKRU\ODWLRQ W H H G W S J D Z G L R O V D K
¶ 7+& SOXV HVWUDGLRO JURXS DWWUKRXP HQW ERW KUW
SKRVSKRU\ODWHG (5. SURWHLQ GHFWH KD V H G ¶ D Q G 7 W & W B E C
WUHDWHG ZLWK ¶ ¶ ¶ 7+& SOX M CHW W L P L G L R L O V K R G W R X V
PDLQWDLQH WKH SKRVSKRU\ODWLRQ R V W O D W H H G (5. SKR X W Y
DEVHQW LQ WKH ¶ H V W U D G L R O H D Q M G P F H Q D G E H H O O W U H D W H
¶ 7+& SOXV HVWUDGLRO KDG DQ H Q H D Q W H S K R V H S Y K R O M O R D W
)LJXUH \$ 7R H[DPLQH LI LQFDVH G X H M Q R W R W D H O D (5HGS
OHYHOV 57 3&5 ZDV UXQ ORRN L Q J L P H W (5 V W D V Q V W L E S W O C
FKDQJH LQ WUDQVFULSW OHYHOV H Z D M V R X O M W Y G H P R Q V W W H D V
¶ 7+& HVWUDGLRO UFRPELQDVMURQ \$ZKRVFSK R R X O D G W E R Q W U L
HQKDQFHG UHFUXLWPHQW RI (5. DQG 65&

7KH +HWHUROLJDQG +\SRWKHVLV

)LJXUH GLVSOD\V D ZRUNLQJ P R G H O R E L Q G L Q J ¶ W R + & 5 D
VDPH WLPH WR R U G H B R X H Q G H (5 H U R K H N K D W H F D X O H J D D G F R Q I R U P
FKDQJH WKDW LV PRUH VWDEOH WKH Q Q H W W W D E G O R W \ E R R X O O
LQFUHDVH LQ WRWDO (5. SURWHLQ R R Y E D W W L R F H R I V V Z H U Q Q H L
WUDQVFULSWLRQDOO\ DFWLYH (5RID(5. ZHOO(5& L Q F F U X H O D G / H
SRWHQWLDO PHFKDQLXPHIRUH FVUKH W P D E G L R O R I ¶ W K H H ¶ V W + & E
(5. WR GLIIHUHQW VHW JHQHV FR P S D Q W L G D W G \ H M S O D I G Q R Q Z
DUH UHJXODWHG O O B V 6. KRXUV

OXWDWLRQDO DQDO\VLV RI WKH (5. /%'+ & RSHOX Q R W W F U R D G L
ELQGLQJ DV D KHWHUROLJDQG

,Q RUGHU WR GHV¶H W + & L Q D V L E L Q G L Q J W D R H (5WDPWH W V H V W U D
/%' RU DQ DOORVWHULF VLWH V S H F X L W D F W D H F L Q R Q D B L Z 6 V F L H O
FRWUDQVIHFWHG ZIGW(5 P X W D O X H F G I (5UIDVUH D Q B X W V H B R V L Q W F
RIDPLQR DFLG VKRZHG QR FKDQJH X W O W H R S R R Q V D P L) Q R X D
VKRZHG D ORVV E G H O W E I D I G U R O V H L E D F X D V Y H L W Q D U G S R O V H Z
WUHDWHG ZLWK ¶ H V W U D G L R O S O) L Q X W H P X W D W L R G R R I D P L Q I
UHVXOWHG LQ D ORVV RI HVWUDGLRO R I O J L Q Z L X F H G ¶ D F W L ¶ L W +
HVWUDGLRO EXWLQ D O W L K W W L Q & L U M O R V H ¶ L J & U H O X W D W L R Q

RI UHVX BW H G D L O O D L O F U H D V H I D Q W D R O V L Y L W B O Z O M U H G D L Q P D
RYH U D O O G H F U H D J X H U H Q D F W L Y L W

)XQFWLRQDO DQDO\VLV HOXFLGDWHV RQH WHHQIR OH\ SDUHQ VLRH
¶ ¶ ¶ 7+& SOXV HVWUDGLRO

7R IXUWKHU H[SORUH WKH KWHHU R D M U D R Q G I R U S R W K ¶ V L ¶ 7D
WRRN DGYDQWDJH RI RXU SUHYLRXV FUGLQJ G W K D W R Q 7+&
WR (5. ZLWK D IROG JUHDWHU DZILQKWD WKDQ O \$ O F H V ¶
FRPSDUHG WR HVWUDGLRO 7DEOH¶ 7+& :HRWHDV R Q H H G V M U K R
ZLWK HVWUDGLRO WKHQ ¶ ¶ ¶ 7+& U V K R X O G P E S H V E Q H Z L R V
¶ 7+& EXW WKH HVWUDGLRO DFWLYD W ¶ R G & Z O O C E H S W H M
ZLWK HVWUDGLRO D G K G L W R L W J S O R E Z H O O V Z H G U R W U H D R X U V
ZLWK HVWUDGLRO ¶ ¶ ¶ 7+& ¶ Q G + & Q F U H D V L O D J O B M H R V
FRPELQDWLRQ DQG 57 3&5 ZDV GRQH L V R Q H I D P X L Q H H . 57 \$
7KH DGGLWLRQ RI ORZ GRVHV RI V W ¶ D G ¶ L R O & G L O G V O R H W S E O H R
LQGXFHG .57 H[SUHVVLRO)QJ R B Q W U D V Z D W W K O R V N H G E
DGGLWLRQ RI ¶ ¶ 7+& LQ D GRVH % G H S K E G H Q M Q B D Q Q V U
WKDW WKH V \ Q H R U P D W L R I Q U R M D W K H W H U D R Q L R J O D Q G Z L W K ¶

¶ ¶ ¶ 7+& ORZHUJH W K H L Q G X R W L R Q E \ H V W U D G L R O

7R GHWHUPLQH LI ¶ ¶ ¶ 7+& L M D Q G M F W R R Q K E I W H W W H D G
FHOOV ZHUH WUHDWHG ZLWK L Q E Q H D R P E L J Q O R M L H R Q F Z I L W K W U
¶ 7+& 7KH DFWLYD W L X R Q H R I 06%) * 5) ¶ X L 57) L J X U H
& D Q G . L 56) L J X U H ' F O H D F L Q H D Q G G H F D X W G H W K Z
DPRQJ WKH JHQHV WKDW ZHUH UHJXODW % G) W K D Q P R V W L 5 Q
ZHUH QRW UHJXODWHG O E \ K R Z W V I D G L R Q K R W E L O Q D W L R Q Z L V
060% D Q G . 57 J H Q H H [S U H V V L R Q D Q G V) * 5 Q G O G H . G L B 6 W Z L W K
0 ¶ ¶ ¶ 7+& G L W H Q R H V Q R R U S O R Q M L Q K H Q J V G H P R Q V W U D V
¶ ¶ 7+& D O O R Z V H H X O D W E L R Q M B B Z H D G R V H I R O G

¶ ¶ ¶ 7+& LQFUHDVHV HVWUDGLRO R E M Q S L Q J D I I L Q L W \ I

7R GHWHUPLQH LI ¶ ¶ ¶ 7+& F D X M H R I D V F W D Q G H R L Q I R L Q G
8 26. RU 8 26 FHOOV ZHUH U H H D W U H G G Z I R V O K D Q G > - 0 ¶
WKH UHDFWLRQ KDG FRPH WR HTXWOLEQVILXPH WKKH DHPDQZM
DQG WRWDO ELQGLQJ ZDV DVVHV @ H G V W ¶ D G ¶ L R Q E L Q G L Q J U
) L J X U H \$ ¶ ¶ ¶ 7+& G L V G V Q B G L R I O D Q J G L Q J W R (5
7KHVH ILQGLQJV GHPRQVWUDWH VRIDELQGLQJ ¶ R + & . H Q K D O

¶ ¶ ¶ 7+& UHJXODWHV JHQHV LQ 0&) FHOOV
7R H[DPLQH LI ¶ ¶ ¶ 7+& EORFNHIGVNLVWQDGLBQ5LQGDGOM
GRQH LQ 0&) FHOOV WUHDWHG IRRQH RRIXUQ ZRWEKLQDWF
HVWUDGLRO (VWUDGLRO DFWLYDWHGLJXJH)LJXUH E\ SR
ZKLFK DUH NQRZQ WDUJHW JHQHV LQ 0&HUYFHGOOR DQV¶
JHQHV 7)) DQG *3; %LJXUH FRPELQDROLZQVRK H¶VWUDQ 7+&
QRW EORFN HVWUDGLROUHQ&D&DWLRIQS DQGVLRQURIDV)HG 7K
UHVXOWV LQGLFDWH WKDW ¶ ¶ O¶W7L+RQFBIYH¶HWLVVXH

¶ ¶ ¶ 7+& WUHDGLROV LQGXFHG XWHHJQH ZHLJKW JDLQ L
7R GHWHUPLQH LID¶ D¶OH¶WR &E O R F IG XWVHW D Q HRZHLQGVX JD
ZHHN ROG IHPDOH RYDULHFWRPL]H Q J P G D H ZHUVHU DWGLRDO
LQFUHDVLQJ GRVHV RI ¶ ¶ ¶ 7+& ZHONRQH)LRXULQ FRPE&V
WLVVXH ZDV GLVVHFWHG RXW DQGLZVHK FRQGVWRG HY WKULFDOM
DQ IROG LQFUHDVH FRPSDUHG WDWFRQVWU D O R Q I H L Q ¶ U H ¶
ZHLJKW E\ IROG LQFUHDVH 7KHOLQFFNUHG VHQ DQ ZKMIQUX QHIG
WKDW ZHUH IROG KLJKHU WKD¶ H¶VW+BDGDROE O R F N ¶ H V ¶
LQGXFHG XWHULQH ZHLJKW JDLQ¶ ZILWK DWHOEIYQ¶LVQWK
¶ ¶ ¶ 7+& DQG HVWUDGLRO

¶ ¶ ¶ 7+& EORFNV HVWUDGLRO LQGXFH XGO D W HRQ QZIL V K
EORFNLQJ HIIHFWV LQ DGLSRVH WLVVXKH LQ PLFH RQ D VR
:KHUHDV EORFNLQV D W D V R Q B E Z O H I S K U ¶ S H + L W E R F D ¶ K V H H Q G R
FDQFHU LV DQ DGYHUVH HIIHFWVRH UPLVQURLIHQW SLWR G X FLPA
HIIHFWV ¶ ¶ ¶ 7+& KDG QR HILHFW RIRQVEKRG P Z P E D K W J R
DGLSRVH WLVVXH SLQHWHQFBIERIHQVWURUG (RQV D)ILQXQH VKRZV
¶ ¶ ¶ 7+& WUHDWHG PLFH KDIGRQJ W D H H H U Q R G I R P S I W U K L H D O L
\$ & ZKHUHDW D W V H U P L G F L R D W G V R R O M Q L S O B O Q F H U H D V H
SUROLIHU DWLRQ V W D W O X V H) W J X H D W H T G + & L S O K X V ¶ H V ¶ W U D G L R O
D V L P L O D U S D W W H U Q W R F R Q W U F H O D V F V X Z I L V R K Q R Q L Q J O M K I H
J O D Q G V) L J X U H H V W S D G & R O R I L Q G X L F R H G I R H U Q H D F H V S U H U U L
\$ / & 1) L J X U H % 6 \$) L S X U H L J X U H & D Q G & D V
H[DPLQH DQG FRPSDUHG EHWZHHQ ¶ V W & D S O L R V O H W W H D D W
WUHDWPHQW ¶ ¶ ¶ 7+& DORQH\ GILQ P Q R W G L Q B Q F M H (N S W
SURGXFHG D PDUNHG DFWLYDWRQERITWKT¶V¶ JH Q H Y Q ZIGLF
WLVVXH 57 3&5 DQDO\VLV ZDV GRQHESR HLDPLQH WKSH HBS
)LJXUH %)DW3 &)DWQGHDD ')LJXUH S)DW3 DQG 6D
ZHUH XS UHJXODWHG E\ D Q G Q W I R O R G Q B L V ¶ S W H V W L L R
\$ H E S D Q G / 3 / Z H U H \ X S G U H J X L O R D Q V R I G L ¶ W K ¶ H V ¶ U D & L Z R O W R
IROG ZKHUHDV W B D H [S D V V G R Z Q U R H R O G D W H G ¶ W R ¶ 7+& D O
UHJXODWHG ERWK \$HES DQG)DW3 E\ DQG IROG

)LJXUH)ORZ FKDUWV FRPSDULQJ FODWRLEDOXVHOG W
LGHQWLI\ QHZ W\SHV RI HVWURJHQV IRU XVH LQ 0+7

(VWUDGLRO

↑ '+&
↑ ↑ 7+&
↑ ↑ ↑ 7+&
↑ ↑ ↑ 7+&
↑ ↑ '+&

)LJXUH 6FUHHQLQJ V\QWKHWLF FKLDFRQHYEWR SRKQGXJ
8 26 FHOOV ZHUH FRWUDQVIHFWHG ZMWHU (WUDQGIHFWWRQC
WUHDWHG ZLWK —0 RI PXOWLSOH GM SQ&VWDQ&PUB&FK
HVVWUDGLRO IRU H QRXH/ D&GOOZEZHUPBNXDFHGLXVWQJ D O
5/8 LV UHODWLYDHF&LG&WDXQRWQWFD&S&H&V&Q&W&D&W&H&V&O&R&W&R
0HDQ “ 6(0 3 YDOXH W WHVW

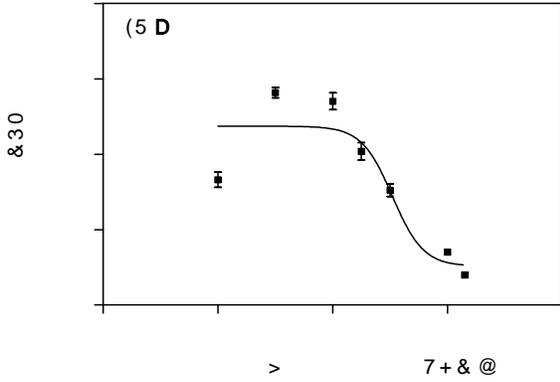
(VWUDGLRO
¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ ¶ 7+& V\QH UJL]H Q WFKHL SHWLRLDGL D G WLQYGL
WN OXFLIHU DVH LQ 8 26 FHO 26 H FSHUOWW Z E W H 5E RRUU D S V I H
WN OXFLIHU DVH D QGH U5.WRUD Q 5 I H \$ W L R I G F H R U O V Z K R U K H W W D I H W
H V W U D G L R O D Q G 0 ¶ ¶ ¶ 7+& Z E B E H O R V H G Q D I R G P E X E D M H I
Z D V P H D V X U H G 5 / 8 L V U H O D W L Y H H O H J K W W X E L R V O R J L E B I O G M U M
E D U V D U H W K H O H D D X H 6 V O D U H 3 Y W W H V W

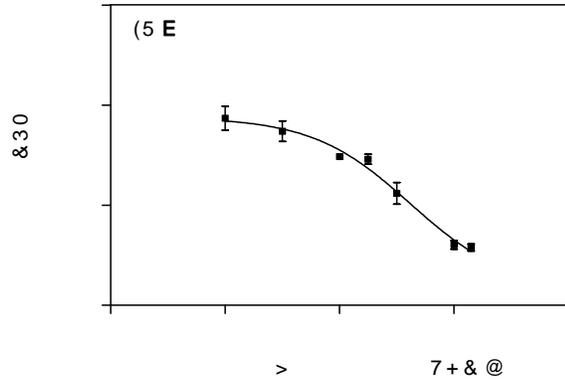
(VWURQH
(VWULRO
¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ ¶ 7+& V\QH UJLJHV QERXFKH GHV(UWQHOX RIG
DFWLYLW\ LQ D 8H2SRFHCHOUV DZMUDH FRWUDQVIHFWHGQZLWK (5
WUHDWHG IRU KRXUV ZLWK Q0¶HV¶W¶R&BORQB RVWLQLRQ
&HOOV ZHUH O\VHG DQG OXFLIHU DVH 'ZDWDPVH DW XUHGS X M V G Q
WULSOLFDDWHV DU(HUWRKH BBDQ " 6(0 W W B V W O X H

\$



%



)LJXUH ¶ ¶ ¶ WR+(5.EDQGV(5 LQGDFRPSHROLDWIDYH ELQGL
 LQ 8 26 (5. DQG8 26H050VRU FHOHQ ZILWIK DQG ZWWIRRXW GR
 KRXUV WR LQGXFVHLRQFHSWRUW DWSHG@LMKWUDGLRO DQG L
 GRVHV 0 0 ¶ ¶ ¶ 7+& IRU UHFRXSUW DW@E RUXQVGRB
 ZDV FRXQWHG XVLQDDWQRTXIFR XQFSEW P/6@XW8RX83W VIRU V
 ELQGLQJ ZDV FDOFXODWHG E\ VXEWRUDFVLEQDQRQJSHFLIOR
 ERXQ@>HVVUDGLRO ZDV XVHGDWLRY@FERLDW@JWRIFRPSDULV
 HVVUDGLRO /RJ,& RI ¶ ¶ ¶ 7+& GIRU (5% DQGSUR[LPDW\$
 GDWD SRLQW LV QXSDMMUGHMIRUPTXDDWLRQV " 6(0

(VWUDGLRO
7DPR[LIHQ
5DOR[LIHQH
¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ ¶ 7+& EHKDYHV DV D XHQH XHH[SFURHVRIQRO
8 26. FHOOV ZHUH ~~KRXLDWZIGWRGR~~ [HF\BEEGBWRRJ LHQ SXHV
&HOOV ZHUH WKHQ WUHDWHG IRU ~~HKRWUDGZIRVOK~~ YHOKL
K\GUR[\WDPR[LIHQ —0 UDOR[LIHQHUDQG FR-DE [QD [WL ¶ 7+&
GDWD SRLQW UHSWLSHLOFDWHEV HQRHUSFDGWDG ISRO QDORQH
¶ ¶ ¶ 7+& SOQG HWDVPRDIGIHRQSDXWH GWWQJ DG(LRUR U HESU V
PHDQ “ 6(0 3 YDOXHV DUH

\$

9

(VWUDGLRO
7DPR[LIHQ
¶ ¶ ¶ 7+&

(VWUDGLRO
5DOR[LIHQH
¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ ¶ 7+& DE XQDYMH FRODURIQXOVWRHG 6JHQH 1.*
8 26. FHOOV ZHUH WUHDWHG IRU HKRHFUHSZLRWKHGSPHFVFOBQ
WUHDWHG ZLWK Q0 HVWUDGLRO —RU ¶DQR[L¶HQB DORQ
FRPELQDWLRQ IRU KRXUV 'DWD QSRFDQHW UH[SHBWHQWW
WDPR[LIHQ SOXV ¶ ¶ ¶ 7+& SQXWRHVEVDUDGDRQ “UH(SUHVH

(VWUDGLRO
¶ ¶ ¶ 7+&

)LJXUH 7KH FRPELQDWRU SOXVXVWUDGHBO\RD ERWK .
DQG 1.* (JHQH H[SUHVVLRQ EHVZHGHODQZHUKRWUMDWHC
ZLWK GR[\F\FOLQH WR LQGXFH UHWHSWZLWK[SQHVVLRQD&HF
¶ ¶ ¶ 7+& DORQH RU LQ FRPELQDWRUDISRLQWV UHRSUHV
WULSOLFDPWHV H[FDORQH UHSUHVHWLQWUHQ “ 6UURU E

(VWUDGLRO
¶ ¶ ¶ 7+&

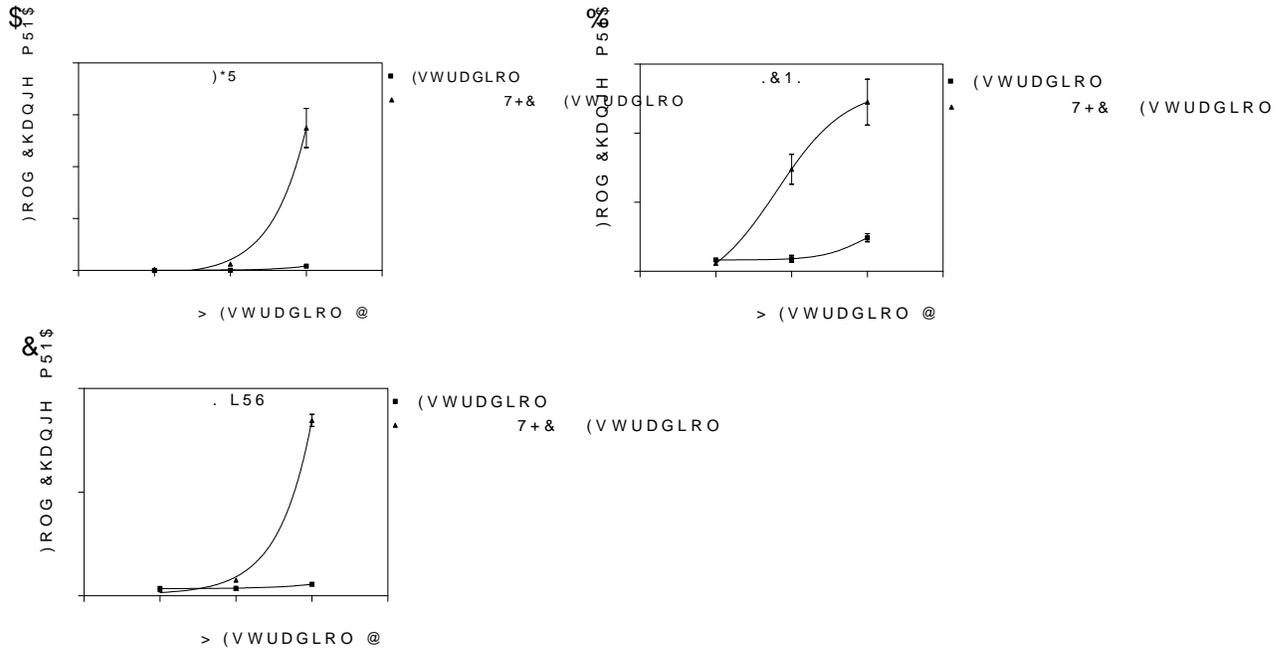
)LJXUH 7RWDQEMJEX\OHWWHGD.GLROU ¶ ¶ ¶ 7+& SOXV
HVWUDGLRO LQ 8 26.8F26.OFHDVV ZKRRUWUKIXUH ZLWK GR[\
WR LQGXFH UNFHBORRSHQSV ZHUHO WIKWQU DGLRDWRIG ZLWK ¶
7+& DORQH RU LQ FDMELSRWQRQUXDEKUGRQWVH QHRWDIØODV
GRZQ E\ HDFK WUHDVPEHQVDDER UGKQJRWLVZLWKJXODWLR
DQG D 3 YDOXH RI ”

7DEOH 7KUH FODVVHV RI JHQH& DSLOK V HJXVDDGLR E\LC
FHOOV DW KRXV2R1 FHUODWZHIQW WUHDWHG IRU FHKRXUV
UHFHSWRU H[SUHVVLQR &HOOV ZHURUWKHQ WUHDWHG+ZLV
LQ FRPELQDWLRQ &ODVV, JQHVV QHSHUHQV JHQHV7Z&LF
SUHVHQFH RI HVWUDGLRO &ODVV UHVNRQ ZDSUHQHQLJH
FRPELQDWLRQ RI ¶ ¶ ¶ 7+& SOXV HXVUDGLROR WQDV¶,
SOXV HVWUDGLROR VUHQVPUHQW LURQZSV HQWUDGLRORU ¶
DORQH ([SUHVVLQR ZDV DVVHVHGLRQ XS UHQGDRULRQRU
YDOXH ”

(VWUDGLRO &RPPRQ

¶ ¶ ¶ 7+&

)LJXUH 9HQ GLDJVLRQ HVKURZLHQWWUK HR IWRHQDHY QREH
UHJXODWHG E\ HVWUDGLRQ +D&RQXVWUDGLRQLRQLTXHO\UH
JQHVV ¶ ¶ ¶ 7+& SOXV HVWUDGLRORVXQVUDGLRQLRQLTXHO\UH
SOXV HVWUDGLRO ERWK VKDUHG DMHQVWHLQ ERBRQHJX
GRZQ UHJXODWLRQ RI IROG RU PRUH DQG D 3 YDOXH ”

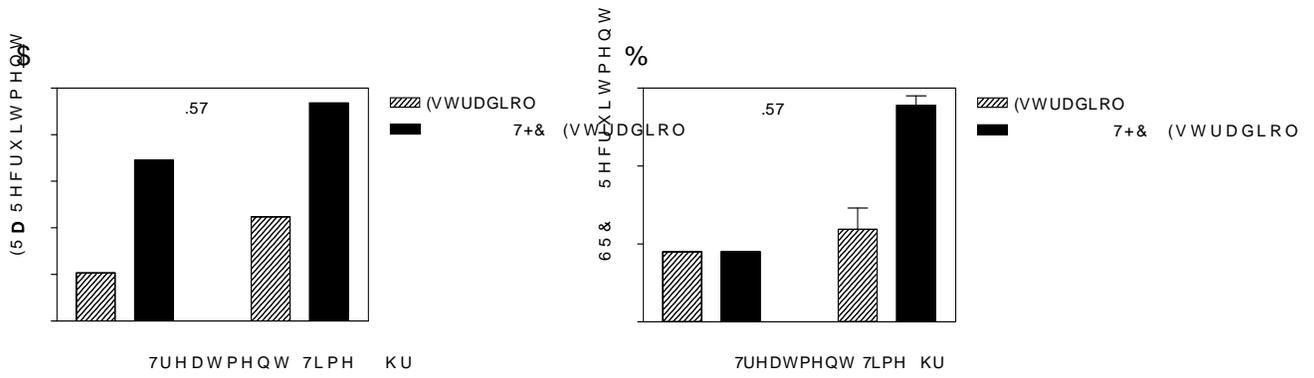


)LJXUH 57 3&5 FRQIRUPDWLRQ RI (SLFHURV) FIDWV
 ZHUH WUHDWHG GRU\F\FKRLXUH VZRWLQGXVFLRQFH&SHURDWZHGZL
 PXOWLSOH GRVHV RI HWWUDGLRO RU LQ FRPELQDWLRQ ZL
 7+& 'DWD SRLQWVJUHISOHWULQVLELW D

(VWUDGLRO
¶ ¶ ¶ 7+&
,&,

)LJXUH %RWK PLFURDUUD\ FODM TX, L UH 3 6, , FUHQXVO ZMUH
WUHDWHG IRU KRXUV ZLWK GR[VLFQ L Q HOVR/ LZHGXF W UHDFV
HVVUDGLRO — 0 ¶ ¶ ¶ 7+& RU Q 0IR 8, D KRQ HV R U DLVQ D F
UHSUHVHQW ELRO(RJLFD E DWUL SOHFV W H VPHDQ “ 6(0

)LJXUH 0RGHO VKRZLQJ WKH SRVSLIEVHLRQFKVDOHILWR RI
¶ 7+& SOXV HVWUDGLRO RQ WKH .57 JHQH SURPRWHU



)LJXUH ¶ ¶ ¶ 7+& SOXV HVW WDBLEB WLF (5 HDQGV 65
 UHFHSWRUV WR WKH SURPERFH QORIZH WUHDWHG ZLWK GF
 WR LQGXFH UHFHSWRUZHLSHUHWUHLRWDHGLRDK—0Q¶ HW¶W ¶ 7+&
 RU LQ FRPELQDWLRQ RRUHLRUV ZHFKLHVZLWOLQNRGOWG HK\GH
 QXFOHDU IUDFWLRQV. ZLGH 65& OISERFVXLRVZHEHLSLWDWH
 XQFURVVOLQNHG IURP '1\$ 57 3&5 ZDVPHQVVRWK RZLQJS (5R
 65& UHFUXLWPHQW (DFK GDWDLSRQQHW \$VRD UHFRUERMRIQRVD
 % KRXU WKDW LV D UHSUHVHQWVWYH¶ R7+& ELRQRHLCDC
 (5. RU 65& (UURU EDUV DUH 0HDQ " 6(0

\$

BBBBB BBBB BBBBBB

(VWUDGLRO
↑ ↑ ↑ 7+&

(5 i

N'D

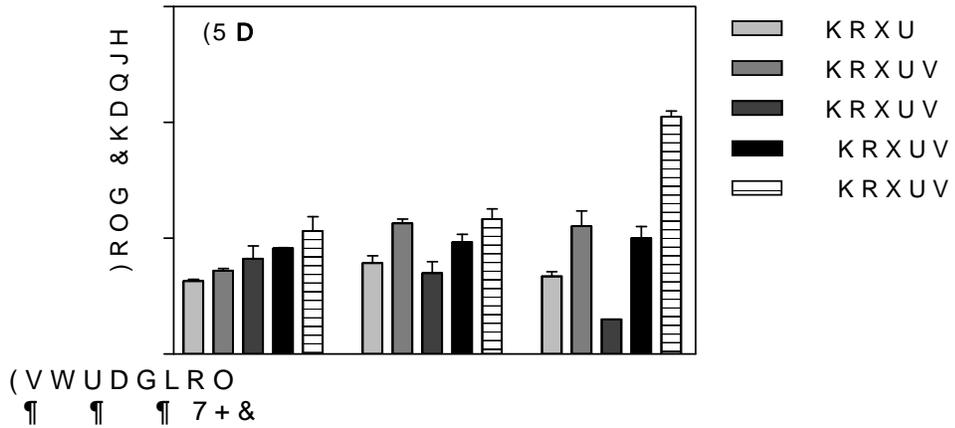
6

N'D

¢ DFWLQ

N'D

%
% P 51 \$



)LJXUH ↑ ↑ H V W U D S I O R O V W D S U G W H V Q (5 . Q V R W D D Q V F U
DFWLYH 6 S K R V S K & U 2 6 0 D F W L O R Q Q / V Z M U W H K B N D W H Z G W R G R [\ F \ P
L Q G X F H U H F H S W R U H H U [S U W U H D L W G & Z R O O K V - Z O 0 H V W U D I G 7 + & D C
L Q F R P E L Q D W L R Q I R U R U K R X U W \$ % R U R W D O (5 . D C
 S K R V S K R U \ O D W H G (5 . O H Y H O V Z H U D Q C O W H U P L Q D F G V Z Q W Z C
D F R Q W U R O I R U S U R R W H L Q (5 . R D G U Z O U M \$ G L S W H O P I Y H O Y X V L Q J \$
'D W D S R L Q W V U H \$ B B O H Q D P S O H \$ U R O B E B O B V I R F O E D W C D U H
O H D Q " 6 (0 %

+HWHUROLDJQG +\SRWKHVLV RI ¶
0HFKDQLVP

)LJXUH
FRPSOH[

0R7G+8CSORV HWUDIG(LRQDELQGLQW HWROLJ

(VWUDGLRO
¶ ¶ ¶ 7+&

)LJXUH 7UDQVIHFWLRQ RI SRLQW.P/%W DWR RIGLQPLQRU DFR
V\QHUJLVWLF DFWZLWLV\TRQ¶DQ¶(3+&S OXUHI D V P U F Q U L O V Z H U H
FRWUDQVIHFWHG ZLWWD(GG/%) (P X N W D H F W H G U D R U H D Q C R X U W Z L
HVVUDGLRO —0 ¶ ¶ ¶ 7+& D O R U C H O R U H L Q Q D F O R P E Q X Q F L W H L R U
ZDV PHDVXUHG XVLQJ D OXPLQRPHWMMUL'SOVL D V M M W U H S R U H V
“ 6(0 3 YDOXH V D U H ” D Q G ” W W H V W

&RPSRXQG	,&
(VWUDGLRO	[0
¶ ¶ 7+&	[0
¶ ¶ ¶ 7+&	[0

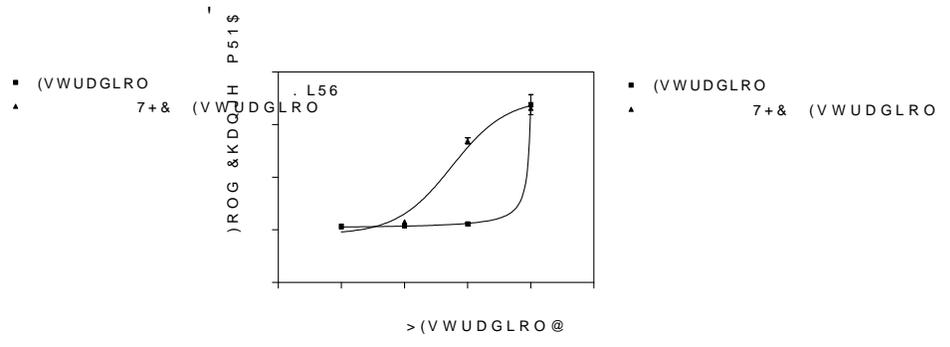
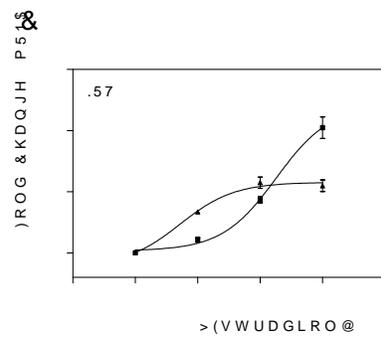
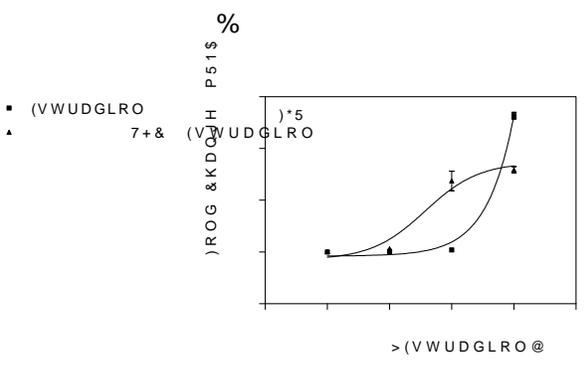
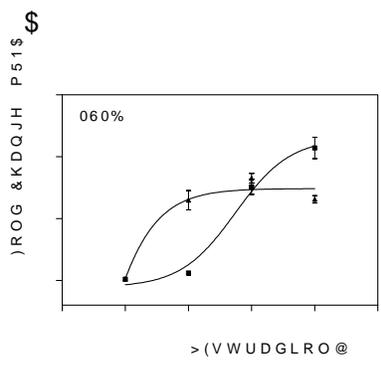
7DEOH 'HULYHG ,& YDOXHV IRU HVWUDGLRO& FRPSHWL
 ELQGLQJ WR (5. LQ, & 20. DDXO VZHUH FDOFXODWHG IURP EL
 FRPSHWLHVWUDGLRO ELQGLQJ DVVD\ LQZBLW. FRIDVWLK
 IRU KRXUV IROORZHG EAVHMDWDBQRROZDQK LQFVHDVLQJ
 ¶ 7+& RU ¶ ¶ ¶ 7+& &HOOV ZHUH&ZDVKZHUZLFRKQW\$DQ
 OLTXLG VFLQWLOODFWERQGERXQWFRSHDHEE0&BRQ

\$

%

(VWUDGLRO
 -0 ¶ ¶ 7+&
 -0 ¶ ¶ 7+&
 -0 ¶ ¶ 7+&
 ¶ ¶ ¶ 7+&

)LJXUH)XQFWLRQDO WHVW IR 8 W&KHFKEWMLZHQJH DQGH
 GR[\F\FOLQH IRU KRXUV DQG WKIRQ WUHDVWHG&ZSOKVLQEQ
 Q0 HVWUDGLRO \$DWLRQVRKHHFWBDEQR0 SOWK LQFUHDVLQ
 ¶ ¶ 7+& % 57L8&ZDDQDQ M WRRQRORNYBQ R[S5HVVL'DWD
 UHSUHVHQW ELRO(RJLFWDEWUWLSDHFWWHWHWHDQ " 6(0



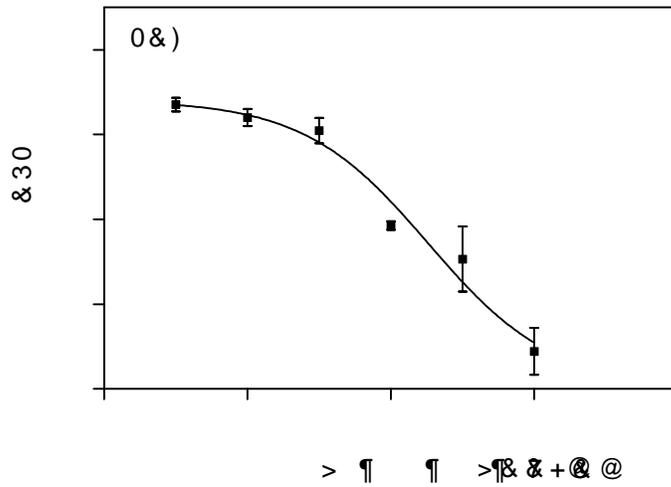
)LJXUH ¶ ¶ ¶ 7+& VKLIWV W&H H Q H R [SUAH V&H Q Q Q L C
 ZHUH WUHDWHG ZU WKKGRX[V F/ F/ R L Q B G U F H V L R H Q H S W R O V H Z H U H
 IRU KRXUV ZLWK LQFUHDV LQJ GRVHSORXIVHDV G P G Q R Q — 0
 ¶ 7+& 7RWDO 51\$ ZDV LVRODWHG DQG VFU X Q Z O R R S U L Q S D D W
 H [S U H V V L R Q R I 060% \$) * 5 % .57 D S R L Q Q V / . U I H 5 6 U H V H Q D W
 W U L S O L F D W H U H Y U I Q R U V E I D W U H U H S “ 6 (0

)LJXUH

0RGHO RI KHWHUROLJDQGLJFDQ OHHYXODVRLHQV

)LJXUH

7KH UROH RI HVWURJH QDWLEQ HDVW FDC



)LJXUH ¶ ¶ ¶ 7+& ELQGV M&R (5F.HLQQV&ZHUFH@QVH DWH
 HVWUDGLRO DQG LQFUHDVLQJ FRQQFHQWV DZWHB QWRRF RFRHO W R
 &HOOV ZHUH ZDVKHG ZLWK %6\$ O\VHG TDQG &FLQZHO DFRU
 6SHFLILF ELQGLQJXZDQJFVQFXDQGLRQ 7MSMIDILEFL EGQGL
 SRLQWV UHSUHVHQVWHRORUURDQVSDUH WKH OHD

'D\
(VWUDGLRO
—0 ¶ ¶ ¶ 7+&
—0 ¶ ¶ ¶ 7+&
—0 ¶ ¶ ¶ 7+&
—0 ¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ FN¶7H&WE¶D¶RGLRO DQSUXFOHGH&D)WLFHFOOV
ZHUH SODWHG LQ HVWURJHQ GHSULLYGHGRPHRULP DQGLS OHDG
¶ 7+& —0 DORQH RU LQ FRPELQDWERXQQ&HGODI ZHUH FO
KHPRF\WRPHWHU VDW SERROSOLEBUBH DUV DUH WKH OHDQ

(VWUDGLRO
¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ ¶ VW&EGLRFFNVLQGXSHBOL&HUBWORQ E\F
* FHOOF\FOR)DUFHOW ZHUHKRXUDWZLWKRUQO—HVWUDGLRO
¶ 7+& DORQH RU LQORPZHQDIWLRQDQHGHW H&HQQGF\F,OVHWDQDOV
GRQH XVLQJ)ORZURVHQWDLRORJULFSDGSDLDHWWKH(OHDC
3 YDOXH ” W WHVW

\$

%

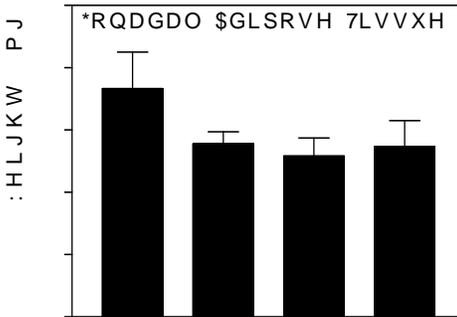
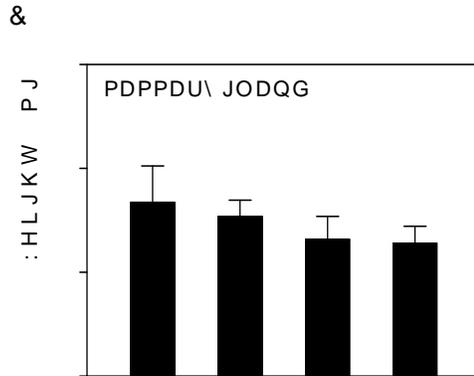
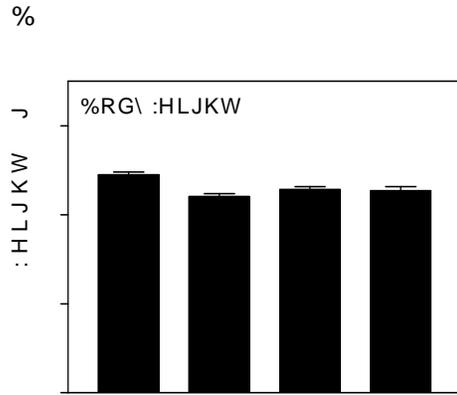
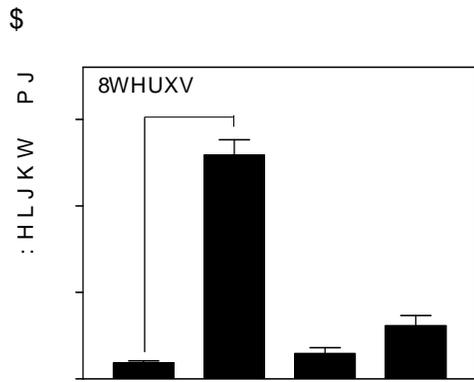
(VWUDGLRO
¶ ¶ ¶ 7+&

&

(VWUDGLRO
¶ ¶ ¶ 7+&

)LJXUH 57 3&5 FRQIRLUPURDVLRLUD\ GDWDFHGRQV IEQO&Y
ZHUH VWULSSHG RGDHWVQRJWQHRUHVVMVDIGGRZLVRK -QO &&
LQ FRPELQDWLRQ IRUS ZKRXVRODPRWHDGFDQSGS57H\$D5 UXQ OR
DW JHQH H[SUHVVLBRQ %I DQG \$(% R&QWVWDH\$SUHVHQW ELF
WULSOLFDPWHV HPHQSWLIR \$ &% UMSRDEWEDQWVDOH WKH OHDQ

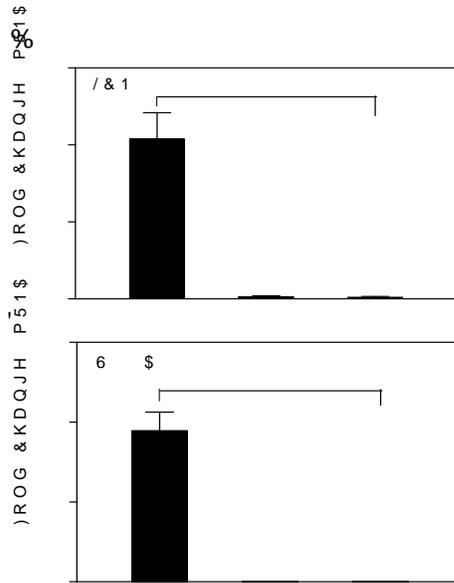
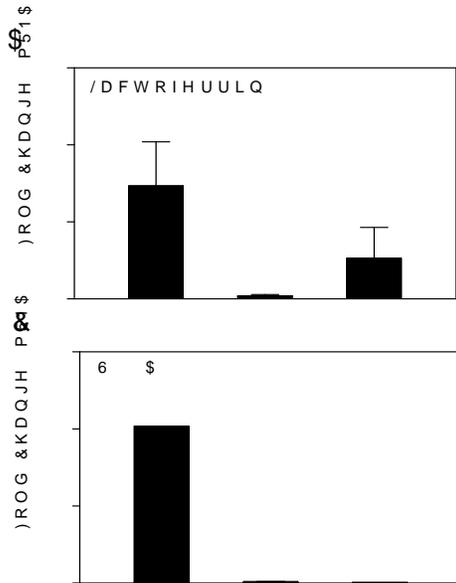
)LJXUH ¶ ¶ FN¶ 7W&HE ERWUDGQROZHLQ&WFHDL&WLQULHPD
DW D UDWLR ZHHN ROG IHPDOH RYDULHFWRPLHHGRQWUHRZH
—J QJ GD\ HVWUDG¶RO¶RU¶ 7+&F&P&Q&D&W&L&R&Q&V&R&I H¶W¶
¶ 7+& DW UDWLRV RI LQH WLVDQGH ZDV F&W&U&H&F
ZHLJKW ZDV PHDVXUHG 'DWD UHSUHVHQWV Q IDQ&R&Q&W&U&F
¶ ¶ 7+& UHSUHVHQWV UHSUHVHQWV QUH ¶U&H&R&U&H&D&Q&V 6(0



(VWUDGLRO

↑ ↑ ↑ 7+&

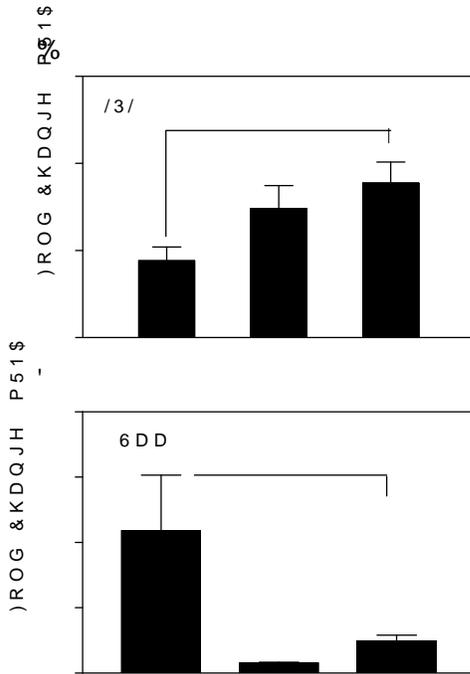
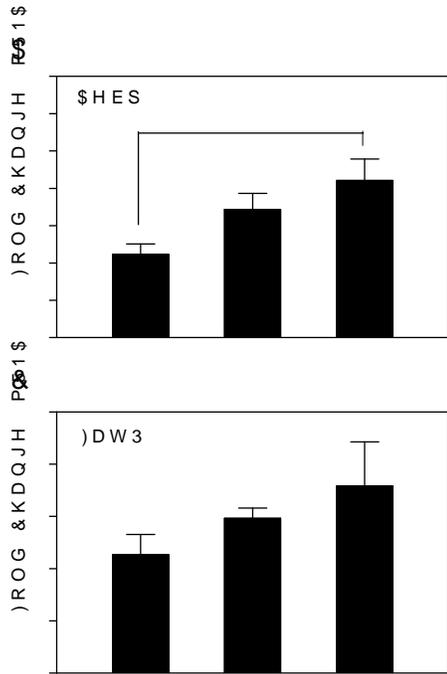
)LJXUH 7LVVXH ZHLJKWV RI PLFMUDGHBW/HG IRU ZFH&
 ↑ ↑ 7+& SOXV HZ/WLNDGORGIOHPDOH RYDULHFWRPL]IG PLFH
 YHKLFOH —J QRGD\—HVGVDGIRPH R U +L&QDFR PELQDWLRQ
 2YHUDOO ERG\ ZHLJKW ZQG RWDVXUHQDSG PDPDU\DRSRVH
 WLVVXH ' ZDV GZVHVKMG' RWD SBLQVWVXRU DXQGHURQDGDO
 Q 'DWD SRLQWV IRU ERG\ ZHLJKW RJSUHVHQRPHQW Q[FH'SV
 PDPPDU\ JODQG ZHLJKW UHSUHVHQWQ HWV/EHDSWRICU ↑ (U
 UHSUHVHQW OHDQ " 6(0



(VWUDGLRO
 ¶ ¶ ¶ 7+&

)LJXUH ¶ ¶ ¶ 7+& EORFNV H V W U D G L R O Z H H Q X R I O G X
 IHPDOH RYDULHFWRPLJHG PLFH ZHUH JWUHQDWG ZH W W U D R G
 —J GD\ ¶ ¶ ¶ 7+& DORQH RU L Q U F R P H L W Q D W W L X R H Q Z I R W U G L Z
 WRWDO 51\$ ZDV FROOHFWHG F'1\$ S U H S D U H Q H D Q S U H V V & B
 ODFWRIHUULQ \$ /&1 % 6 \$ & D U H S U H V H Q W E D R V D R S B E D
 H[FHSW HVWUDGLRO WUHDWPHQW I R Z L W D Q G 6 (U \$ R Z L E W K U Q
 0HDQ " 6(0

)LJXUH ¶ ¶FN ¶7+&WEDGLRO LOGXIFOG SIQGRIPHHWDWLR
ZHHN ROG IHPDOH RYDULHFWRPLJHGHRLFØHZH\$H WUHDVQH
HVWUDGLRO % RU —J GDI ¶ ¶DVLR+Q '& IÐORQZHHRUVL
WLVVXH VDP SOHV ZHUH GLVVHFWHBEHIGG LQQGRVPIFOVLR
UHSUHVHQWV RQH ELRORJLFDO VDP SPOH E+R VJLIFDIOGWDUL SO
WDNHQ DW ; RLO LPPHUVLRQ



(VWUDGLRO

¶ ¶ ¶ 7+&

)LJXUH \$GLSRVH SWLHMXLR QHLOH KLFMWWUDGLRIG ZLW¶ ¶
 ¶ ¶ ¶ 7+& SOXVZHMWURDGLRDPDOH RYDULHFWRPLJHG PLFI
 YHKLFOH —J QJRGD\—HGDUDGIRPH ¶ 7+&QDFRPELQDWLRQ
 \$GLSRVH WLVVXH ZDV GLVVHFWHG DQGHWRWHDG DQ\$ ZDV3&5
 ORRNLQJ DW JHQH\$HSSJH/3VLRQ)¶ \$DQG 6 'DWD SRLQWV IF
 UHSUHVHQW Q 'DWD SRLQWV IRUH)DWBHQWQGU6SDHYNQW D
 (UURU EDUV UHSUHVHQW OHDQ " 6(0

&+\$37(5)285

'LVFXVLRQ DQG &RQFOXVLRQ

0HQRS DXVH LV DVVRFLDWHG ZLWK P DOWKLS WHI ODKRKJHW WHQLE
GU\QHV V DQG ORQJ WHUP GLVHDVH D LQQ F D Q G L Q S H R V W I B R S
(VWURJHQV DUH HIIHFWLYH DW UHG XE X W J DW K H D M V R V P L S D W R H
LQFUHDVH LQ EUHD V D Q F Q G H D Q G R I O M P O G D F I O R W M J R J & X Q U D U H U
IRU RQO\ VKRUW WHUP XVH ZKLFK SURPHEDQW V K W R I Q R F I U F R F
DVVRFLDWHG ZLWK PHQRS DXVH 7KH DSUR O H I G H L D D W H L G H E H (5 H F
PDGH DQ\ HVWURJHQV WKDW ELQG HWR W (B . V Q R H W F X S J S H H D Q L Q H
KRUPRQH WKHUDS\ +RZHYHU VW X I G I L F W M Q R G I L F D W H R W K D W
ZHLJKW JDLQ DQG GLDEHWHV DUH D D W B R R W G K D W H H G U E H D (W H
GLOHPPD WR GLVFRYHU VDIHU HVWURJHQV S R V K L S E F O M K W R
HVWURJHQV WKDW ELQG WR (5 . D O O R G J S Z I L W K L R Q V U Z K G E R O F R
WKH FOLQLFDO R O I H F K W H R E M H V F W W H Y B I L R I W R K H G H Q W L X G I D Q (5 .
ZKLFK ZH GHILQH DV D FRPSRXQG W K D K W H E L V Q G D V G W R O (5 . R V E
PDJQLWXGH DQG SDWWHUQ RI J H Q R Z W W J S D W V V I H G I L Q I F H O S M
(5 . F R D J R Q L V W Z K L F K F D Q P R G X O D W H V H D Q G U S D G M R B O R Q J L (5 D O

7UDQVIHFWRQ G D F W D H Z D W K W H G V W W R P X H O Q L F S O I F W L Y Q L W K H R M I L F
FRPSRXQGV 2XU UHVXOWV VKRZHGWV D G W R Q L Q G X F H G & U V I S C
RQ DQ (5 (L Q F H O O V R Y H U H [S U H V V L H Q L F 5 . D E W W K R W W R Q L V S O
RWKHU WULK\GUR[\FKDOFRQH V W I H G I D O + & R D Q L G V S O D I H Q I Q +
DFWLYLW\ RQ WKHLU RZQ EXW W R W W H R F K D O F U R Q G I L R D Q W I D J F
WKH RQO\ H [D P L Q F R Q F K D L O F R Q O B O V K W M U R [S O L P R X X S Q J R Q Q G D
K\GUR[\O JURXS % H F D X V H W K H R V F R H Q W V Z G M L W L K H G U B [F R D
SRVLWLRQ LW LV OLNHO\ WKDW W R Q L V W K D F W R L Y D W L V 7 L P S R V
GLK\GUR[\FKDOFRQH F R B L F Q Q R W D E W S O I D W L Q K R Z H Y Y W L Q J W R
' + & K D G Q R D F W L Y L W \ E X W Z K H Q W K M L Q I G K I R [I P K S R V L R V L O F
GLVSOD\HG HVWURJHQV D F W L Y L W G R I G U R V O R Z I Q R X S H I U R P G I
WR I I 7 + & U H V X O W H G L Q D Q M O J R I Q L V V K I S U D F [W Q Y I L M R X S
WR D I K \ G U R [\ O S R V L W L R Q W K H F K D F O V L R Y Q M \ Q R Z K H V R H I H L
GHPRQVWUDWH WKDW E \ P R Y L Q J W R K H S B Q L F K I D R Q J H R I W K K H D I F W
FKDOFRQH FRPSRXQGV W R W R B W H L P S R D W W D V K I R I I I O H S F X O D U
ZKLFK LV VLPLODU WR HVWUDGLRODWH WKDW 7 K I L V I R E I H 7 + &
ILW LQ WKH OLJDQG ELQGLQJ SRFDNHWR IRWKHUH F M D O R F I R I Q H
LVROLTXLULWLJHQLQ ZKLFK KDV D N P R O Z I G X O R D U E L Z H G J M R E R R
(5 > @

I I I 7 + & ZDV DOVR LQDFWLYH RQ LKRVZHRZHU LQ W F H O Q M
HVWUDGLRO LQGXFHG UHSRUWHU I F W I L Y + L S V L V 7 Q R W G H H P O R H W
RU (5 7 K H I D F W W K D W I I I Z E W K O S / R L Q G W F D W M Q V U W K
SRWHQWLDWH WKH D W Q R I Z Q I D Q F W L V S P R O I D V K H S K E Z L (O O E H D Q
FOLQLFDO SURSHUWLW LV @ P S R I M P O R X Q G V L W K O W L F D Q D O V
DFWLYLW\ RI (5 . E H F D X V H W K H H I I V F X H / D R Q H V P K H G L E R V Q H H G D
7KHUHIRUH DQ L G H G E H F R R S R X Q G V Z X D F O F D Q D E O R F N 5 W K E H S U
HIIHFWV RI (5 . Z K W O H S U Q V H I L F Y L D Q H O I H F K W H V R U D (G V I H F W L R
LQGLFDWH WKDW I R W I H Q I V Z B O E V Q G K I G D W H I W H F S U R G X F

¶ ¶ ¶ 7+& GHPRQVWUDWHV WKDJR QKDWIER QR QRXQD W 5 F
IDFW WKDW ¶ \$UHV F Q F HL QR WKV KHU DG MLO LFKD BU HWK W HV W
VXSSRUWV WKH LGHD WKDW (5. LVQRG R SWE RD JB QM K WU GROR
GLVWLQFW IURP WKH DJRQLVW FRVQIR UFDWDLJRO L QG XFRQ ER UH
E\ WKH 6(50V

OLFURDUUD\ DQDO\ WLR SDG YG L W D S W E M D Y H V ¶ D V ¶ D Q + (5. FR
EHFDXVH LW FKDQJHV WKH HVWUDGHR Q V P H L G / L Z W E G H V W H E
WDPR[LIHQ RU UDOR B H J K O B V E L O R F R R V O K I Q H V ¶ E \ ¶ V W & D G X Q L T
LW LWVHOI RQO\ UHJXODWHV JHQRILDXWRGUBRDBWLFBD
HVWUDGLROW 7 ¶ H ¶ D F ¶ Q W H S D F K I H H M S R I D V G L R K R F W O E M K Z L Y L Q J
DQ DJRQLVW RU DQWDJRQLVW GHPRQEVH E O D W H M L W K G W D V ¶ D
\$OWKRXJK ¶ ¶ ¶ 7+& ELQGV WR U 5 . V S R Q V H W R Q H V K H U R V
H[SUHVVLQR DQG RYHUDOO JHQH H[S U K H V F I K R Q J H K D Q J H H R F F M
IRXQG RQ WKH PLFURDUUD\ FRXOG EFRQ & B U W R J H F R P E L I Q J H G
5HJDUGOHVV RI WKH HIIHFWV EHLQW V G X M K M R X S W I I R B U A H R O U H V H
UHTXLUH (5. EHF D X H W H J X O R D W L R I Q J R V F H X D W J P V R Z M V S K L , R ¶ 7 + &
DQG HVWUDGLRO

7KH DELOLW\ RI ¶ ¶ ¶ 7+& WR E Q B Q M K U W K H K H (5 W U D G Z L R O
IURP HVWUDGLRO DQG 6(50V VROLGRILHWWW R H H Q L D W H (G F H F
¶ ¶ ¶ 7+& %HFDXVH ZH GLG QRWL RFR S S R U I H O R Y H I U D D X F H
¶ 7+& DQG HVWUDGLRO LQ PXOWLS Q K H F W H O H O U O R L Q H V R W L W K H
SURILOH LV D E M Q H O R I L D O M Q M V S O H I U M M D R I X W I S X H O R L Q H D W L R Q
VKRZHG WKDW WDPR[LIHQ DQG UDOR GL U H Q J X Z B W H G D E W L S H H F
JHQHV , W LV Z H O O N Q R Z Q W K D W I Z Q H F R P E D R D W L H R Q D Z Q G K U B I O
EHKDYH DV DQWDJRQLVWV EORFN L Q Z K I V O H U D B U R O D I W L Q X F J H
RZQ > @ ¶ ¶ ¶ 7+& GRHV QRW E H K W Y R I Q D V D V Q D G R R Q V J H
LQ 8 26 FHOOV LQVWHDG LW FKDQJH W W K R Q R S B W D V O H O U Q
GHPRQVWUDWLQJ LWV XQLTXH FRDR R Q D V W W X G W H V L Z M O Q X Q M
GHWHUPLQH LI ¶ D V ¶ D Q ¶ (5 + & B B J R Q O O W W L S H R V D K H G L F Q D Q L P D

\$OWKRXJK H[SORULQJ WKH PHFKDQLX R R V D B V G R R O R R Q ¶ W
UHJXODWHG F O H W H , V , W U B Q H W K E V D Q Q M H W L S R Q R H H V O M B R O W V C
WKR VH J H Q H V L V X Q N Q R Z Q) R U W S Q R U L H Q D V V Q H Z F H G F K I D L Q L H V C
XWLOL]LQJ WKH .57 SURPRWHU D V D D P S G H P O U A K (5 (. 5 Q G L S U
ZKLFK LV UHJXO D W B G V E Q H U V M U H D G R E R Q V K H ¶ D Q G L + & L R W Z D V S U
SXEOLVKHG E\ RXU ODE WKDW HVW(5 D G L R O V K I Q K D Q F H G H V K H
WUHDWPHQW Z L M R X H V W U @ G Z R E F R U ¶ E L Q D W & R Q Q B I H ¶ W U D G L R
D V \ Q H U J L V W L F U H F U X L W P H Q W R I (5 W K H Q S U S R P R V R H D F V R L Y H V
UHJXODWHG JHQH . Q 7 S U R K E G H D L Q B V A P H R M D E V O L R H Q F R D Q ¶ ¶
RQ HVWUDGLRO JHQH V \ Q H U J \ E X R U G R H Z Q H R O V H H U S I O X D Q W W L K
LQFUHDVLQJ UHFULXW L R P H S R W V R U E S F U W K V W H V Q M H B H R L W K U H U S
WR WKH SURPRWHUV RI QHZO\ U W J K O O D V ¶ H G ¶ J H ¶ Q 7 + & U W G L V B E
S F R D F W L Y D W R U V W R U H J X O D W R D W H G O H I R G E W V D S F U R X I Q M W
JHQH UHJXODWLRQ REVHUYHG RQ WKH PLFURDUUD\

SUREOHP LQ ZRPHQ GXWLKQDVP HQRZSIOXSIHURFOX OBIWHQV 0WVWG V
WLVVXH SK\VLORORUGXPRWHR VRKBIQ DOBLQ HF0Q0 JHH[VS U2HXUW ILQGLQ
WKDW ¶ ¶ ¶ 7+& FRXOG EH DGPDOERQM HZLHV GK WARK FHQRDSO
WKH JHQH H[SU00VLRQ0SIBOL0H HFWWU R UHHQVGR JHQVR0MDWLQ
¶ ¶ ¶ 7+& DORQHQBIXW KRXWU R JRDQ P XVF KHQRIZ ZIUOLEN IRU
HQGRPHWULDO FDQFHU

\$OWKRXJK ¶ ¶ ¶ 7+& V\QHUJLJHWVZRV KL0V8W26D GILFOOD RQLJ
EORFNV HVWUDGLRVLRLQGLXCFH0)SURIOHODVUWHF B0F7HUYHG WKD
7+& ERXQG WR HQGRJHQRXV (5. LQ 0&H) SUFFOLOMUBWWRQWDQ
WR EORFN HVWUDGLRO LQGXFHG SUV0DIWUDWLRQ R17F+00
HVWUDGLRO LQGXFH0G F\AORH6WSJKD0H0V LR0R00K0R/XUH QLV0ZILQ
LQ 8 26 FHOOV ¶ ¶ ¶ 7+& GLGYDWRWRQ[KILVELWDDQW0JURHJLV
¶ ¶ 7+& GLG QRMOE0HRFXOBWWR0Q0L5(03; DQ)GRIS UHJXODW
H[SUHVVLQR RI *3; DQG 7)) LQ WKXJISZHHVZIQFHI BE0HVWURDQ
¶ ¶ ¶ 7+& EORFINQGXVWVGDSGURROXIQHJED0HLRVR0ZHVZHWPILQH L
E\ VWXG\LQJ RQO\ D IHZ HVWUDGLROWKIDXWDDVHG ¶HQHV
FRPELQDWLRQRIQ0H¶W\UDF0X0R0DWH0H0D0W0G0L0D0VHWRIJHQHV
RYHUDOO SUROLIHUWLYH SURIMORH0RQ0DQWU0SGURRO0IHUR0PWL
VWXGLHV DUH0R0H0G0W0GLW0S0R0M0S0LELOLW\

:H REVHUYHG WKDW ¶ ¶ ¶ 7+& 0DQH0KIDSURIMOKH LHQWU0B0G
DQG ZKLWH DGLSRVQH VLVVX0HIL0GL0R00S0W0RHL0H0S0U2HVDULLHFWR
WUHDWHG ZLWK HVWUDGLRO KDGGRQHLV0BUB0DVH0D00S0W0R0L0
ZDV EORFNHG E\ ¶ ¶ ¶ 7+& ¶ D0L0R00700&0GX0F0VR0E0R0FNH0C
WKH XWHUXV 7KHVH REVHUYDWLRQ0V D0X0J0D0V(05. VDKDWDJRQLV
WLVVXH %HFDXVH5LWVLVH0GRZQ0V0K0H0V0B0P0H0G0L0D0V0L0S0U0R0L0
SRVVLEOH WKDW ¶ ¶ ¶ 7+& LV ERK0Y0H0Q0J0LW0DQ0X0Q0D0H0V
UDWLR RI HVWUDGLRO WR ¶FRX0G0D0F0V0&0D0K0D0D0Q0W0D0J0R0
HVWUDGLRO ELQ00Q0V0K0D0W0L0¶P0R0L0E0H0Q0D0X0&0Q0J0D0R0D0Q0D0Q0D0J0R0Q0
PRGXODWRU WKDW00K0D0Q0H0H0V0S0K0H0VR0K0L0R0D0S0GR0Q0F0M0Z0K0L0F0O0X0F0
REVHUYLQJ RQO\ D IHZ HVWUDGLROPLH0X0D0W0M0B0S0H00S0X0F0
SUROLIHUWLYHUM0H0F0W0D0F0W0Q0Y0D0K0H0L0Q0W0P0V0X0E0X0V0L0N0H0L0V0E0H0F0D0X0V0
XWHUXV PDLQO\ H[SUHVHV (5. > @

2XU VWXG\ DOVR GHPRQVWUDWHG W0D0M0Q0¶H0S0U0¶V0V0&0R00K00
PRXVH ZKLWH DGLSER0H0Q0V0L0V0P0R0Q0V0W0D0V0H0F00R0X0W0W0K0R0X0V0H0WKDW
RI HVWUDGLRO RQ ZKLWH DGLSRVHI R0V0L0V0H0X0Y0H00S0U0W0K0D0V0G0L0D0W0H0G0
JHQHV LQ ZKLWHQ0D0G0W0K0D0W0¶L0V0V0X0H0V0K00P0R0S0X0H0D0W0L0R0Q0RI0W0K0
6XUSULVLQJO\ ¶ ¶ ¶ 7+& UHJXODW0V00D00S00D00S0\0H0Q00Q0D0W00
DGGLWLYH HIIHFV ZLWK HVWUDG¶R0¶70K0H0V0H0&0LHV000W0V0Y0G0H0F0
WLVVXH DQG WKDW LW LV DEOH MR0Q0P0R0Q00000W0G00V0K0H0V0V0H0Q0H0
WRJHWKHU ZLWK LWV HIIHFV LQ WIK0W0X0VR0H000V0H0I0F0V0¶Q070
E\ LQFUHDVLQJ WKHS E[0S0D0W00L0D0Q0R0I00S0U0R0G0I0B00B0W0N0V0H0H0I0H0
XWHUXV \$OWKRXJKH0Z0M0D0E0J0L0X0Q0D0E0K0D0W0W0R0K0H0V0R0H0F0Q0D0Q0H0V0H[0S0U0
PHGLDWHG WKURXJK (5. WKH SURPQ0GL00V00S0W0R0GL0R00R0Z0ID0U0D0
LQYHVWLJDWLRQ

&21&/86,21

7UDQVIHFWLRQ ELQGLQJ &K,3 :HWXGILUHQV%LQR8W2BQGHUHQVH
ZLWK SUROLIHUHWLRQ VWXGLHV LQ 0& 7F&KOW GEPXQVW
WKDW GLVWLQJXLVK LW IURP WKG F&UQHFDW OJRTKLW DFQGLY
 7+& DUH EHVW GHVFULEHG DV DQHU5.OE RVDWG Q LDVFW LBYH FD
SRWHQWLDWHV WKH HIIHFWV RI HVWUDGLRO WQ VRFKHODHVN
JHQHV DW SK\VLRXURJLEDDQQMYHXQVH 77+ &WSDWG XFH 7 LWV F
HIIHFWV E\ IRUPLQJ DQ (5. KHWHURKHLDDQGLFRPBOHIVDQGL
WR FDXVH D VKLIW LQ WKH (& RLRQW 7DGLRQ 7H&XDDGW H
LQGXFHV JOREDQSHUHWVDBQRKDDQHGHLLQW&Q6W FHWQVHVWU
ZLWKRXW FDXVLQJ&SURQLHHDV DWEIRDBBUVFXGQMV \$QLPRQVWU
 7 7+& EORFNVFHGSUWRGLR Q ULQGLR Q HDQCG JHURZ RPKDMM LD U
LQ XWHULQH WLWVXHVZKULDBVFRQJHODMVLURQ LQ DGLSRVH WL
EHHQ XVHG IRU RYHU \HDUV EYLWNFELQLHGHQVXW XEGLQHVILV
ZKHQ XVHG FRQLQXRXVO\ IRU D RQDJDWLRFIL DWHVGHUZHDWK F
%HFDXVH PFK IHZHU HOLJLEOH ZRPGQV B UGH WHDOR Q JV D+H UW
IRU ORQJ WHUP XVH 7 7 7+&DM[KLLEH SRWHHQWUDO SDYRR
)LUVW 7 7 7D+&DPQJ(KWFRFDWRQKMSWUROLOKULEWWRQ RI E
DOWHULQJ WKH[SDWWHUG BHRQGVJKWTEH7DE-08H WR EH XVI
WKH HIIHFWV RIHQVZRILHQXODMKHQJQEHGHIRUH BMLJHQVXV HV
DUH NQRZQ WR LQEUHDVW WQIG HQVQRIRUHQV URXDW UFDQXGWW V K
 7+& DFWLYDWHV (5 ZKLFK PLJKWVEHWDXSXRQQLSIBSMLY
HVWURJHQV LQ WKH EUHDVW XWHVXLQ VQGVRSURSRV DODV
FRDJRQLVWV VXFK DV 7 7 7+&IFLVWWRUHQN HIRHUQV+D
FKURQLF FRQGLWLRQV DVVRFLDWHG ZLWK PHQRSDXVH

5 () (5 (1 & (6

+DMLUDKLPNKDQ \$ & 6LPPOHU < Q<X'DQI LNR5OISQ G%UO
'LHW] *) 3DXOL 5 % YDQEvaluation of the Estrogenic Activity of
Licorice Species in Comparison with Hops in Botanicals for Menopausal Symptoms
3XEOLF /LEUDU\ RI 6FISHQFH
3DUXWKL\LO 6 \$DI&HYULR , 0 & R & HDOL (& 6KMEstrogen
Receptor Causes a G2 Cell Cycle Arrest by Inhibiting CDK1 Activity through the
Regulation of Cyclin B1, GADD45A and BTG2% UH D V W & D Q F H U 5 H V H D U F K
S J

0HUVHUHDX - (1 /HY\ 5 (6WDXE & K R Z % D \$ J H W W N H 7 0-
7DJOLDIHUUL , & R K H Q /) %Mitigation of High-Dose
Highly Selective Estrogen Receptor Beta Agonist ROHF XODU DQG & HOOXODU
S J

+HLQH 3 \$ - \$ 7D\ORU * \$, Z D P R W n e a s e d % A d i p o s e D K Q 3
Tissue in Male and Female Estrogen Receptor-alpha Knockout Mice R F H H G L Q J V R I
1DWLRQDO \$ F D G H P \ R I 6 F L B Q F H 8 6 \$
/HY\ 1 ; = K D R + D M B Q J 3 % S H H Q M u l t i p l e T r a n s c r i p t i o n
Factor Elements Collaborate with Estrogen Receptor Alpha to Activate an Inducible
Estrogen Response Element in the NKG2E Gene Q G R F U L Q R O R J \ S J

'D\ D Q * 0 / X S L H Q \$ \$ X J H U 6 \$ Q J K L H O U H : - 5 R F
. D W] H Q H O O H Q E R J a n d R o s i t a n e D i f f e r i n T h e i r F u n c t i o n a l
Interactions with Aspartate 351 of Estrogen Receptor 0 R O H F X O D U 3 K D U P D F R O

% U] R] R Z V N L \$ 0 \$ 3 L N H = ' D X W H O U V W U R P E E / D 2 6 P D Q %
* U H H Q H - \$ * X V W D I M o l e c u l a r B a s i s o f A g o n i s m a n d A n t a g o n i s m i n t h e
Oestrogen Receptor 1 D W X U H S J

% D O O / - 1 / H Y \ ; = K D R & * K H I Q L Q \$ 0 5 7 D J N O H L D 7 I 3 U 6 S
* /) L U H V W R Q H ' C e l l T y p e L a n d E s t r o g e n R e c e p t o r - S u b t y p e S p e c i f i c
Regulation of Selective Estrogen Receptor Modulator Regulatory Elements O H F X O D U
& H O O X O D U (Q G R F U L Q R O R J \

& Y R U R \$ & 7] D J ' D U D N L R / P) R U V 6 H 3 P [U X V & K L / H D O W a d Q
Roles of Unliganded and Liganded Estrogen Receptors in Transcriptional Repression
0 R O H F X O D U & H O O S J

& K H Q ' 7 5 L H G O (: D V K E U R R N 3 0 \ 3 D F A c t i v a t i o n o f & R R P E H
Estrogen Receptor by S118 Phosphorylation Involves Ligand-Dependent Interaction
with TFIIH and Participation of CDK7 0 R O H F X O D U % L R O R J \ S J W K H & H C

/ L X 6 6 - + D C o o p e r a t i v e A c t i v a t i o n o f G e n e E x p r e s s i o n b y A g o n i s t s a n d
Antagonists Mediated by Estrogen Receptor Heteroligand Dimer Complexes 0 R O H F X O D U
3 K D U P D F R O R J \ S J

& R X V H -) - / L Q G] H \ . * U D Q G L H D F T i s s u e D i s t r i b u t i o n I V V R Q
and Quantitative Analysis of Estrogen Receptor-Alpha and Estrogen Receptor-Beta

(ER) Messenger Ribonucleic Acid in the Wild-type and ERalpha-knockout Mouse
(Q G R F U L Q R O R J \ S J