

eolf-othd-000002
SEQUENCE LISTING

<110> Crucell Holland B.V.
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Custers, Jerome Hubertina Henricus Victor
Scheper, Gerrit Christiaan
Oosterhuis, Koen
Uil, Taco Gilles
Khan, Selina

<120> Therapeutic HPV16 vaccines

<130> 0248 WO 00 ORD

<160> 19

<170> PatentIn version 3.5

<210> 1

<211> 328

<212> PRT

<213> Artificial Sequence

<220>

<223> HPV16-E6E7SH designer polypeptide

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Arg Lys Leu Pro Gln Leu Cys Thr Glu Leu Gln Thr Thr Ile His Asp
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Ile Ile Leu Glu Cys Val Tyr Cys Lys Gln Gln Leu Glu Asp Glu Ile
35 40 45

Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala His Tyr Asn Ile
50 55 60

Val Thr Phe Cys Cys Lys Cys Asp Ser Thr Leu Arg Leu Cys Val Gln
65 70 75 80

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Ser Thr His Val Asp Ile Arg Thr Leu Glu Asp Leu Leu Met Gly Thr
85 90 95

Leu Gly Ile Val Cys Pro Ile Cys Ser Gln Lys Pro Gly Thr Thr Leu
100 105 110

Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys Ile
115 120 125

Asn Cys Gln Lys Pro Leu Cys Pro Glu Glu Lys Gln Arg His Leu Asp
130 135 140

Lys Lys Gln Arg Phe His Asn Ile Arg Gly Arg Trp Thr Gly Arg Cys
145 150 155 160

Met Ser Cys Cys Arg Ser Ser Arg Thr Arg Arg Glu Thr Gln Met His
165 170 175

Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu
180 185 190

Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser Glu Glu
195 200 205

Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala
210 215 220

His Tyr Asn Ile Val Thr Phe Cys Cys Gln Leu Cys Thr Glu Leu Gln
225 230 235 240

Thr Thr Ile His Asp Ile Ile Leu Glu Cys Val Tyr Cys Lys Gln Gln
245 250 255

Leu Leu Arg Arg Glu Val Tyr Asp Phe Ala Phe Arg Asp Leu Cys Ile
260 265 270

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Val Tyr Arg Asp Gly Asn Pro Tyr Ala Val Cys Asp Lys Cys Leu Lys
275 280 285

Phe Tyr Ser Lys Ile Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu Tyr
290 295 300

Gly Thr Thr Leu Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu
305 310 315 320

Ile Arg Cys Ile Asn Cys Gln Lys
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<210> 2

<211> 990

<212> DNA

<213> Artificial Sequence

<220>

<223> nt sequence encoding HPV16-E6E7SH designer polypeptide

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cactacaata tcgtgacctt ctgctgcaag tgcgacagca ccctgcggct gtgcgtgcag	240
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cagctgaacg acagcagcga ggaagaggac gagattgacg gacccgctgg acaggccgag	660
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gccgtgtgcg acaagtgcct gaagttctac agcaagatca gcgagtaccg gcactactgc	900
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<210> 3
 <211> 693
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 3

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			20					25					30		

Trp	Lys	His	Met	Arg	Leu	Glu	Cys	Ala	Ile	Tyr	Tyr	Lys	Ala	Arg	Glu
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Met	Gly	Phe	Lys	His	Ile	Asn	His	Gln	Val	Val	Pro	Thr	Leu	Ala	Val
	50					55					60				

Ser	Lys	Asn	Lys	Ala	Leu	Gln	Ala	Ile	Glu	Leu	Gln	Leu	Thr	Leu	Glu
65					70				75						80

Thr	Ile	Tyr	Asn	Ser	Gln	Tyr	Ser	Asn	Glu	Lys	Trp	Thr	Leu	Gln	Asp
			85					90						95	

Val	Ser	Leu	Glu	Val	Tyr	Leu	Thr	Ala	Pro	Thr	Gly	Cys	Ile	Lys	Lys
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His Gly Tyr Thr Val Glu Val Gln Phe Asp Gly Asp Ile Cys Asn Thr
115 120 125

Met His Tyr Thr Asn Trp Thr His Ile Tyr Ile Cys Glu Glu Ala Ser
130 135 140

Val Thr Val Val Glu Gly Gln Val Asp Tyr Tyr Gly Leu Tyr Tyr Val
145 150 155 160

His Glu Gly Ile Arg Thr Tyr Phe Val Gln Phe Lys Asp Asp Ala Glu
165 170 175

Lys Tyr Ser Lys Asn Lys Val Trp Glu Val His Ala Gly Gly Gln Val
180 185 190

Ile Leu Cys Pro Thr Ser Val Phe Ser Ser Asn Glu Val Ser Ser Pro
195 200 205

Glu Ile Ile Arg Gln His Leu Ala Asn His Pro Ala Ala Thr His Thr
210 215 220

Lys Ala Val Ala Leu Gly Thr Glu Glu Thr Gln Thr Thr Ile Gln Arg
225 230 235 240

Pro Arg Ser Glu Pro Asp Thr Gly Asn Pro Cys His Thr Thr Lys Leu
245 250 255

Leu His Arg Asp Ser Val Asp Ser Ala Pro Ile Leu Thr Ala Phe Asn
260 265 270

Ser Ser His Lys Gly Arg Ile Asn Cys Asn Ser Asn Thr Thr Pro Ile
275 280 285

Val His Leu Lys Val Asp Ala Asn Thr Leu Met Arg Leu Arg Tyr Arg
290 295 300

Phe Lys Lys His Cys Thr Leu Tyr Thr Ala Val Ser Ser Thr Trp His
305 310 315 320

Trp Thr Gly His Asn Val Lys His Lys Ser Ala Ile Val Thr Leu Thr
325 330 335

Tyr Asp Ser Glu Trp Gln Arg Asp Gln Phe Leu Ser Gln Val Lys Ile
340 345 350

Pro Lys Thr Ile Thr Val Ser Thr Gly Phe Met Ser Ile Met His Gln
355 360 365

Lys Arg Thr Ala Met Phe Gln Asp Pro Gln Glu Arg Pro Arg Lys Leu
370 375 380

Pro Gln Leu Cys Thr Glu Leu Gln Thr Thr Ile His Asp Ile Ile Leu
385 390 395 400

Glu Cys Val Tyr Cys Lys Gln Gln Leu Glu Asp Glu Ile Asp Gly Pro
405 410 415

Ala Gly Gln Ala Glu Pro Asp Arg Ala His Tyr Asn Ile Val Thr Phe
420 425 430

Cys Cys Lys Cys Asp Ser Thr Leu Arg Leu Cys Val Gln Ser Thr His
435 440 445

Val Asp Ile Arg Thr Leu Glu Asp Leu Leu Met Gly Thr Leu Gly Ile
450 455 460

Val Cys Pro Ile Cys Ser Gln Lys Pro Gly Thr Thr Leu Glu Gln Gln
465 470 475 480

Tyr Asn Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys Ile Asn Cys Gln
485 490 495

Lys Pro Leu Cys Pro Glu Glu Lys Gln Arg His Leu Asp Lys Lys Gln
500 505 510

Arg Phe His Asn Ile Arg Gly Arg Trp Thr Gly Arg Cys Met Ser Cys
515 520 525

Cys Arg Ser Ser Arg Thr Arg Arg Glu Thr Gln Met His Gly Asp Thr
530 535 540

Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr Thr Asp
545 550 555 560

Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser Glu Glu Glu Asp Glu
565 570 575

Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala His Tyr Asn
580 585 590

Ile Val Thr Phe Cys Cys Gln Leu Cys Thr Glu Leu Gln Thr Thr Ile
595 600 605

His Asp Ile Ile Leu Glu Cys Val Tyr Cys Lys Gln Gln Leu Leu Arg
610 615 620

Arg Glu Val Tyr Asp Phe Ala Phe Arg Asp Leu Cys Ile Val Tyr Arg
625 630 635 640

Asp Gly Asn Pro Tyr Ala Val Cys Asp Lys Cys Leu Lys Phe Tyr Ser
645 650 655

Lys Ile Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu Tyr Gly Thr Thr
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Leu Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys
675 680 685

Ile Asn Cys Gln Lys
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<210> 4
<211> 2085
<212> DNA
<213> Artificial Sequence

<220>
<223> nt sequence encoding HPV16 E2E6E7SH designer polypeptide

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gccatctact acaaggccag agagatgggc ttcaagcaca tcaaccacca ggtgggtgccc 180
accctggccg tgtccaagaa caaggccctg caggccatcg agctgcagct gaccctggaa 240
accatctaca acagccagta cagcaacgag aagtggaccc tgcaggacgt gtccctggaa 300
gtgtacctga ccgctccac cggtgcatc aagaaacacg gctacaccgt ggaagtgcag 360
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gccacccaca caaaggccgt ggccctgggc accgaggaaa ccagaccac catccagcgg 720
cccagaagcg agcccgacac cggcaatccc tgccacacca ccaagctgct gcaccgggac 780
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tggaccggcc acaacgtgaa gcacaagagc gccatcgtga ccctgacctc cgacagcgag 1020

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cccagaaagc tgccccagct gtgcaccgag ctgcagacca ccatccacga catcatcctg	1200
gaatgcgtgt actgcaagca gcagctggaa gatgagatcg acggccctgc tggccaggcc	1260
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ctctgtgata tgctgattcg ctgtatcaat tgtcagaagt gataa	2085

<210> 5
 <211> 693
 <212> PRT
 <213> Artificial Sequence

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 <223> HPV16 E6E7E2SH designer polypeptide

 <400> 5

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Arg Lys Leu Pro Gln Leu Cys Thr Glu Leu Gln Thr Thr Ile His Asp
20 25 30

Ile Ile Leu Glu Cys Val Tyr Cys Lys Gln Gln Leu Glu Asp Glu Ile
35 40 45

Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala His Tyr Asn Ile
50 55 60

Val Thr Phe Cys Cys Lys Cys Asp Ser Thr Leu Arg Leu Cys Val Gln
65 70 75 80

Ser Thr His Val Asp Ile Arg Thr Leu Glu Asp Leu Leu Met Gly Thr
85 90 95

Leu Gly Ile Val Cys Pro Ile Cys Ser Gln Lys Pro Gly Thr Thr Leu
100 105 110

Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys Ile
115 120 125

Asn Cys Gln Lys Pro Leu Cys Pro Glu Glu Lys Gln Arg His Leu Asp
130 135 140

Lys Lys Gln Arg Phe His Asn Ile Arg Gly Arg Trp Thr Gly Arg Cys
145 150 155 160

Met Ser Cys Cys Arg Ser Ser Arg Thr Arg Arg Glu Thr Gln Met His
165 170 175

Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu
180 185 190

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Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser Glu Glu
195 200 205

Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala
210 215 220

His Tyr Asn Ile Val Thr Phe Cys Cys Gln Leu Cys Thr Glu Leu Gln
225 230 235 240

Thr Thr Ile His Asp Ile Ile Leu Glu Cys Val Tyr Cys Lys Gln Gln
245 250 255

Leu Leu Arg Arg Glu Val Tyr Asp Phe Ala Phe Arg Asp Leu Cys Ile
260 265 270

Val Tyr Arg Asp Gly Asn Pro Tyr Ala Val Cys Asp Lys Cys Leu Lys
275 280 285

Phe Tyr Ser Lys Ile Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu Tyr
290 295 300

Gly Thr Thr Leu Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu
305 310 315 320

Ile Arg Cys Ile Asn Cys Gln Lys Met Glu Thr Leu Cys Gln Arg Leu
325 330 335

Asn Val Cys Gln Asp Lys Ile Leu Thr His Tyr Glu Asn Asp Ser Thr
340 345 350

Asp Leu Arg Asp His Ile Asp Tyr Trp Lys His Met Arg Leu Glu Cys
355 360 365

Ala Ile Tyr Tyr Lys Ala Arg Glu Met Gly Phe Lys His Ile Asn His
370 375 380

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Gln Val Val Pro Thr Leu Ala Val Ser Lys Asn Lys Ala Leu Gln Ala
385 390 395 400

Ile Glu Leu Gln Leu Thr Leu Glu Thr Ile Tyr Asn Ser Gln Tyr Ser
405 410 415

Asn Glu Lys Trp Thr Leu Gln Asp Val Ser Leu Glu Val Tyr Leu Thr
420 425 430

Ala Pro Thr Gly Cys Ile Lys Lys His Gly Tyr Thr Val Glu Val Gln
435 440 445

Phe Asp Gly Asp Ile Cys Asn Thr Met His Tyr Thr Asn Trp Thr His
450 455 460

Ile Tyr Ile Cys Glu Glu Ala Ser Val Thr Val Val Glu Gly Gln Val
465 470 475 480

Asp Tyr Tyr Gly Leu Tyr Tyr Val His Glu Gly Ile Arg Thr Tyr Phe
485 490 495

Val Gln Phe Lys Asp Asp Ala Glu Lys Tyr Ser Lys Asn Lys Val Trp
500 505 510

Glu Val His Ala Gly Gly Gln Val Ile Leu Cys Pro Thr Ser Val Phe
515 520 525

Ser Ser Asn Glu Val Ser Ser Pro Glu Ile Ile Arg Gln His Leu Ala
530 535 540

Asn His Pro Ala Ala Thr His Thr Lys Ala Val Ala Leu Gly Thr Glu
545 550 555 560

Glu Thr Gln Thr Thr Ile Gln Arg Pro Arg Ser Glu Pro Asp Thr Gly
565 570 575

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Asn Pro Cys His Thr Thr Lys Leu Leu His Arg Asp Ser Val Asp Ser
580 585 590

Ala Pro Ile Leu Thr Ala Phe Asn Ser Ser His Lys Gly Arg Ile Asn
595 600 605

Cys Asn Ser Asn Thr Thr Pro Ile Val His Leu Lys Val Asp Ala Asn
610 615 620

Thr Leu Met Arg Leu Arg Tyr Arg Phe Lys Lys His Cys Thr Leu Tyr
625 630 635 640

Thr Ala Val Ser Ser Thr Trp His Trp Thr Gly His Asn Val Lys His
645 650 655

Lys Ser Ala Ile Val Thr Leu Thr Tyr Asp Ser Glu Trp Gln Arg Asp
660 665 670

Gln Phe Leu Ser Gln Val Lys Ile Pro Lys Thr Ile Thr Val Ser Thr
675 680 685

Gly Phe Met Ser Ile
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<210> 6
<211> 2085
<212> DNA
<213> Artificial Sequence

<220>
<223> nt sequence encoding HPV16 E6E7E2SH designer polypeptide

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gactactacg gcctgtacta cgtgcacgag ggcacccgga cctacttcgt gcagttcaag	1500
gacgacgccg agaagtacag caagaacaaa gtgtgggagg tgcacgctgg cggccaggtc	1560
atcctgtgcc ccaccagcgt gttcagcagc aacgagggtgt ccagccccga gatcatccgg	1620
cagcacctgg ccaatcacc tgccgccacc cacacaaagg ccgtggccct gggcaccgag	1680

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gtgaccctga cctacgacag cgagtggcag cgggaccagt tcctgagcca ggtcaaaatc 2040
ccaagacca tcaccgtgtc caccggcttc atgagcatct gataa 2085

<210> 7
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> IgE leader peptide

<400> 7

Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
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His Ser

<210> 8
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> nt sequence encoding IgE leader peptide

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<210> 9
<211> 21

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<212> PRT
<213> Artificial Sequence

<220>
<223> HAVT20 leader peptide

<400> 9

Met Ala Cys Pro Gly Phe Leu Trp Ala Leu Val Ile Ser Thr Cys Leu
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Glu Phe Ser Met Ala
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<210> 10
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> nt sequence encoding HAVT20 leader peptide

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gcc 63

<210> 11
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> 2xTetO-containing sequence

<400> 11
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<210> 12
<211> 28
<212> DNA
<213> Artificial Sequence

<220>

<223> CuO-containing sequence

<400> 12

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28

<210> 13

<211> 829

<212> DNA

<213> Artificial Sequence

<220>

<223> CMV promoter

<400> 13

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aacattaccg ccatgttgac attgattatt gactagttat taatagtaat caattacggg 180

gtcattagtt catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc 240

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cgccccattg acgcaaatgg gcggtaggcg tgtacgggtg gaggtctata taagcagagc 720

tcgttttagtg aaccgtcaga tcgcctggag acgcatcca cgctgttttg acctccatag 780

aagacaccgg gaccgatcca gcctccgcgg ccgggaacgg tgcattgga 829

<210> 14

<211> 657

<212> DNA

<213> Artificial Sequence

<220>

<223> nt sequence encoding TetR polypeptide

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gataggcacc atactcactt ttgcccttta gaaggggaaa gctggcaaga ttttttacgt	240
aataacgcta aaagtttttag atgtgcttta ctaagtcatc gcgatggagc aaaagtacat	300
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Lys	Leu	Gly	Val	Glu	Gln	Pro	Thr	Leu	Tyr	Trp	His	Val	Lys	Asn	Lys
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Arg Ala Leu Leu Asp Ala Leu Ala Ile Glu Met Leu Asp Arg His His
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Thr His Phe Cys Pro Leu Glu Gly Glu Ser Trp Gln Asp Phe Leu Arg
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Asn Asn Ala Lys Ser Phe Arg Cys Ala Leu Leu Ser His Arg Asp Gly
85 90 95

Ala Lys Val His Leu Gly Thr Arg Pro Thr Glu Lys Gln Tyr Glu Thr
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Leu Glu Asn Gln Leu Ala Phe Leu Cys Gln Gln Gly Phe Ser Leu Glu
115 120 125

Asn Ala Leu Tyr Ala Leu Ser Ala Val Gly His Phe Thr Leu Gly Cys
130 135 140

Val Leu Glu Asp Gln Glu His Gln Val Ala Lys Glu Glu Arg Glu Thr
145 150 155 160

Pro Thr Thr Asp Ser Met Pro Pro Leu Leu Arg Gln Ala Ile Glu Leu
165 170 175

Phe Asp His Gln Gly Ala Glu Pro Ala Phe Leu Phe Gly Leu Glu Leu
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Ile Ile Cys Gly Leu Glu Lys Gln Leu Lys Cys Glu Ser Gly Ser Ala
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Tyr Ser Gly Ser Arg Glu Phe Arg Ser Tyr
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<212> DNA

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<223> nt sequence encoding CymR polypeptide

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<223> CymR polypeptide

<400> 17

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Gly Lys Leu Ile Ala Ala Ala Leu Gly Val Leu Arg Glu Lys Gly Tyr
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Gly Ala Gln Ser His His Phe Pro Thr Lys Leu Glu Leu Leu Leu Ala
50 55 60

Thr Phe Glu Trp Leu Tyr Glu Gln Ile Thr Glu Arg Ser Arg Ala Arg
65 70 75 80

Leu Ala Lys Leu Lys Pro Glu Asp Asp Val Ile Gln Gln Met Leu Asp
85 90 95

Asp Ala Ala Glu Phe Phe Leu Asp Asp Asp Phe Ser Ile Ser Leu Asp
100 105 110

Leu Ile Val Ala Ala Asp Arg Asp Pro Ala Leu Arg Glu Gly Ile Gln
115 120 125

Arg Thr Val Glu Arg Asn Arg Phe Val Val Glu Asp Met Trp Leu Gly
130 135 140

Val Leu Val Ser Arg Gly Leu Ser Arg Asp Asp Ala Glu Asp Ile Leu
145 150 155 160

Trp Leu Ile Phe Asn Ser Val Arg Gly Leu Ala Val Arg Ser Leu Trp
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Ile Ala Arg Glu Arg Tyr Ala Lys Phe Lys Arg
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<223> HPV16 E6 aa41-65

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<223> HPV16 E7 aa43-77

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20 25 30

Asp Ile Arg
35