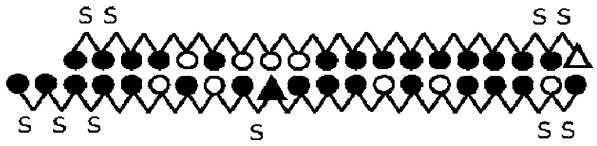
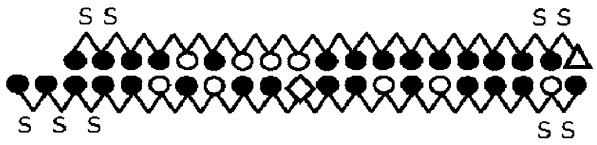
[図1]

NNN-xxx.41DU

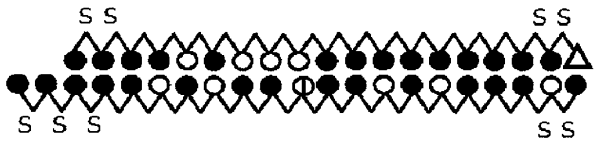
NNN-xxx.42DU



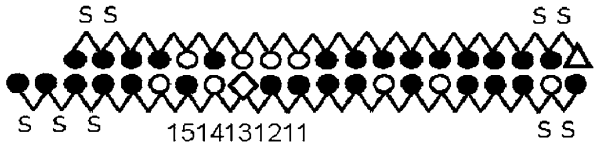
NNN-xxx.43DU



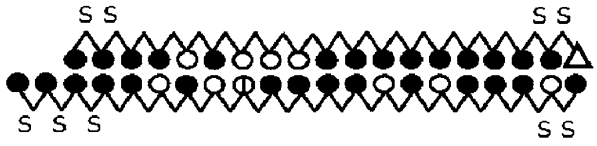
NNN-xxx.44DU



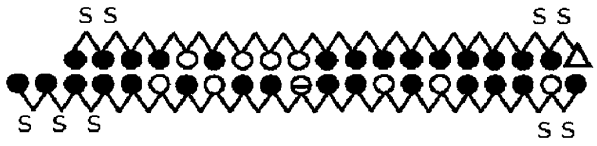
NNN-xxx.45DU



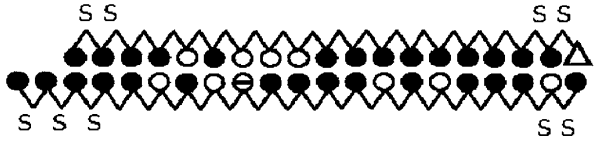
NNN-xxx.46DU



NNN-xxx.47DU

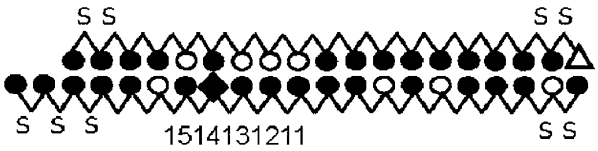


NNN-xxx.48DU

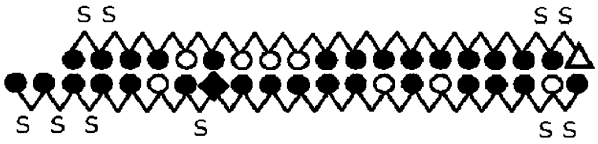


[図2]

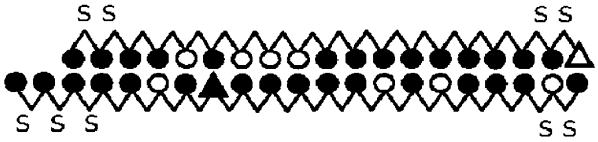
NNN-xxx.56DU



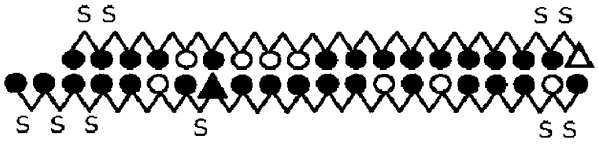
NNN-xxx.57DU



NNN-xxx.58DU

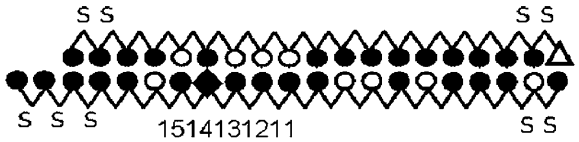


NNN-xxx.59DU

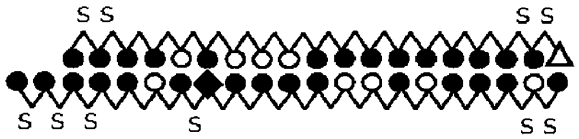


[図3]

NNN-xxx.61DU

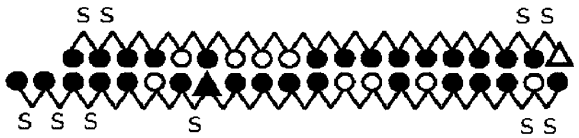


NNN-xxx.62DU



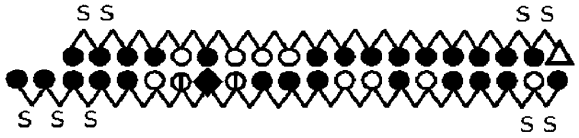
NNN-xxx.63DU

NNN-xxx.64DU



NNN-xxx.66DU

NNN-xxx.67DU



NNN-xxx.68DU

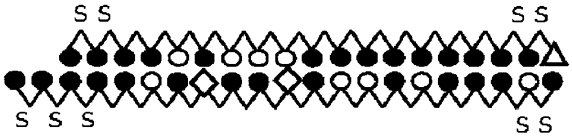
NNN-xxx.69DU

[図4]

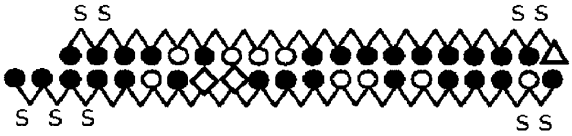
NNN-xxx.70DU

NNN-xxx.71DU

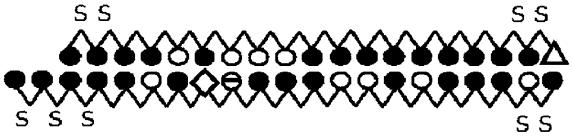
NNN-xxx.72DU



NNN-xxx.73DU

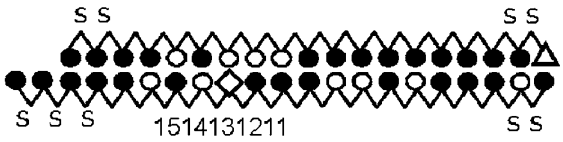


NNN-xxx.74DU

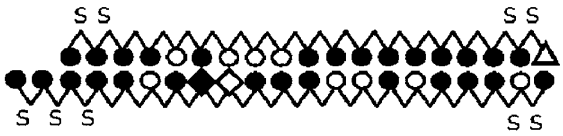


[図5]

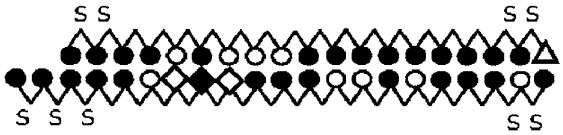
NNN-xxx.75DU



NNN-xxx.76DU

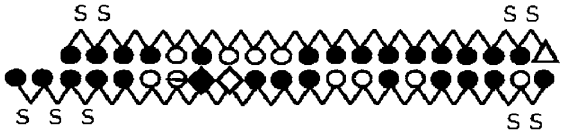


NNN-xxx.77DU

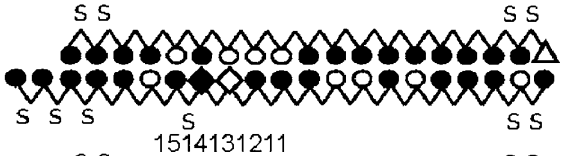


NNN-xxx.78DU

NNN-xxx.79DU

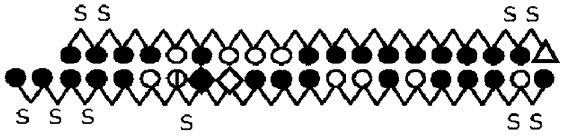


NNN-xxx.80DU



NNN-xxx.81DU

NNN-xxx.82DU

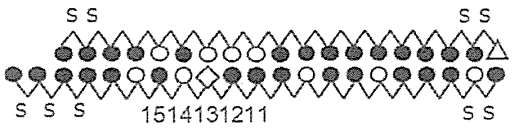


NNN-xxx.83DU

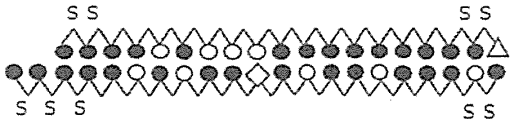
NNN-xxx.84DU

[図6]

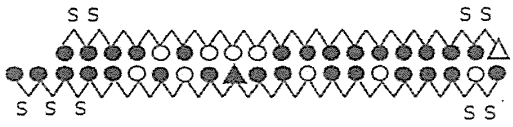
NNN-xxx.85DU



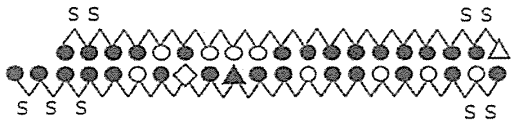
NNN-xxx.86DU



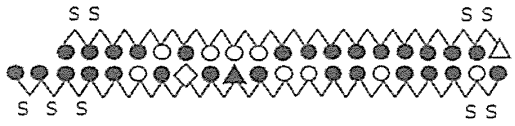
NNN-xxx.87DU



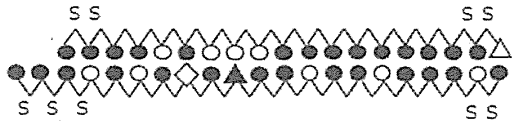
NNN-xxx.88DU



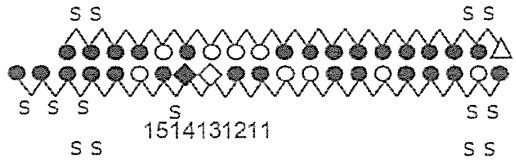
NNN-xxx.89DU



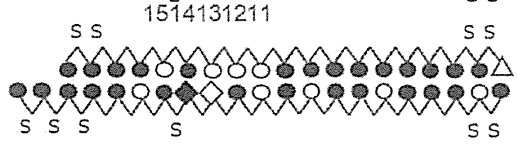
NNN-xxx.90DU



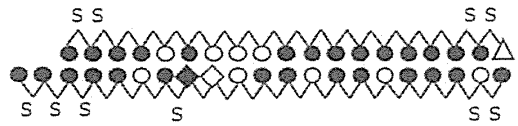
NNN-xxx.91DU



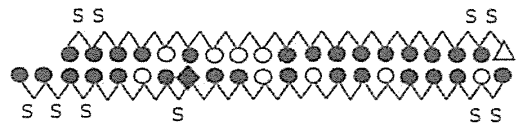
NNN-xxx.92DU



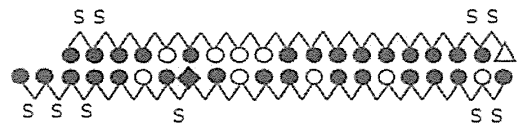
NNN-xxx.93DU



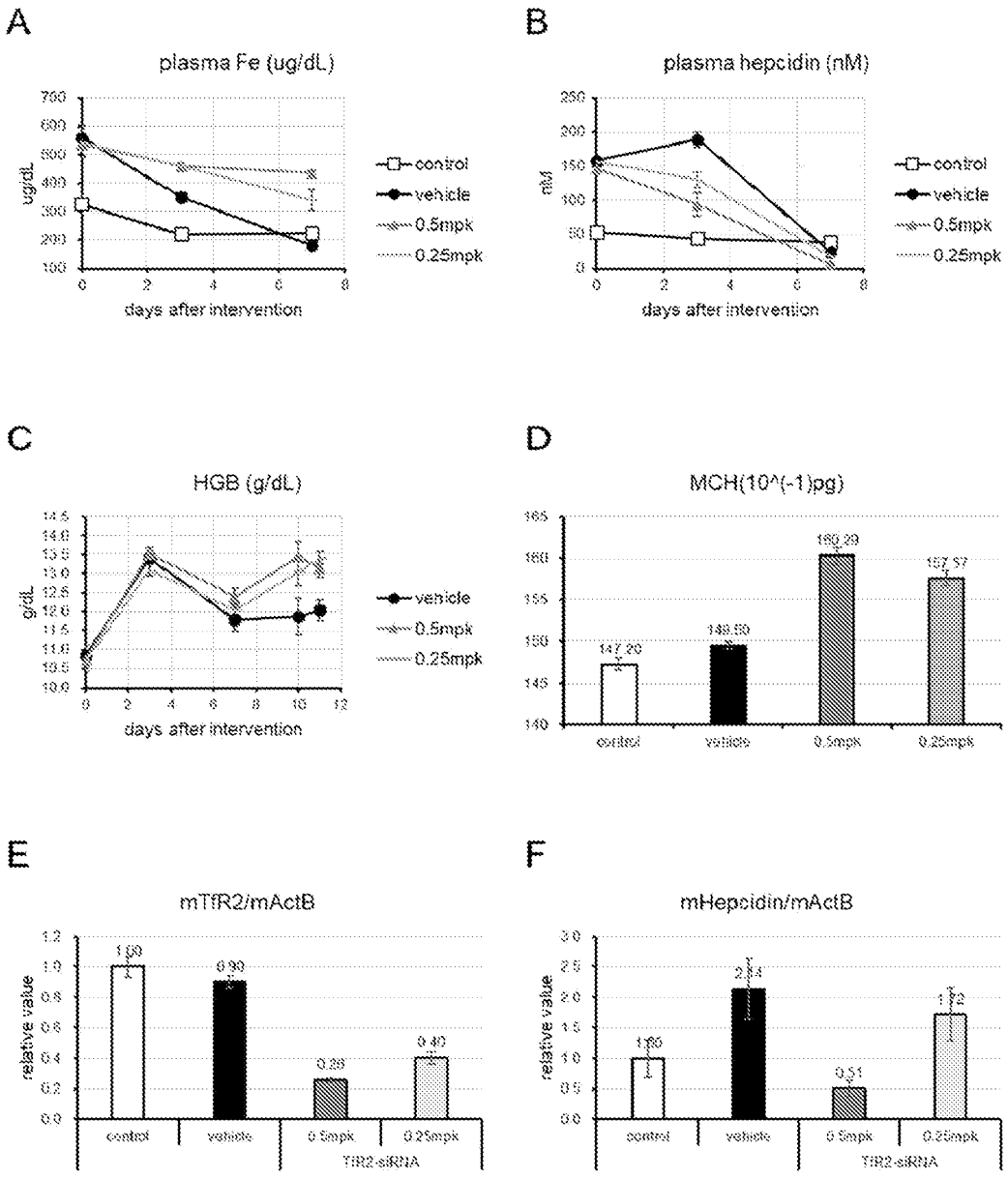
NNN-xxx.94DU



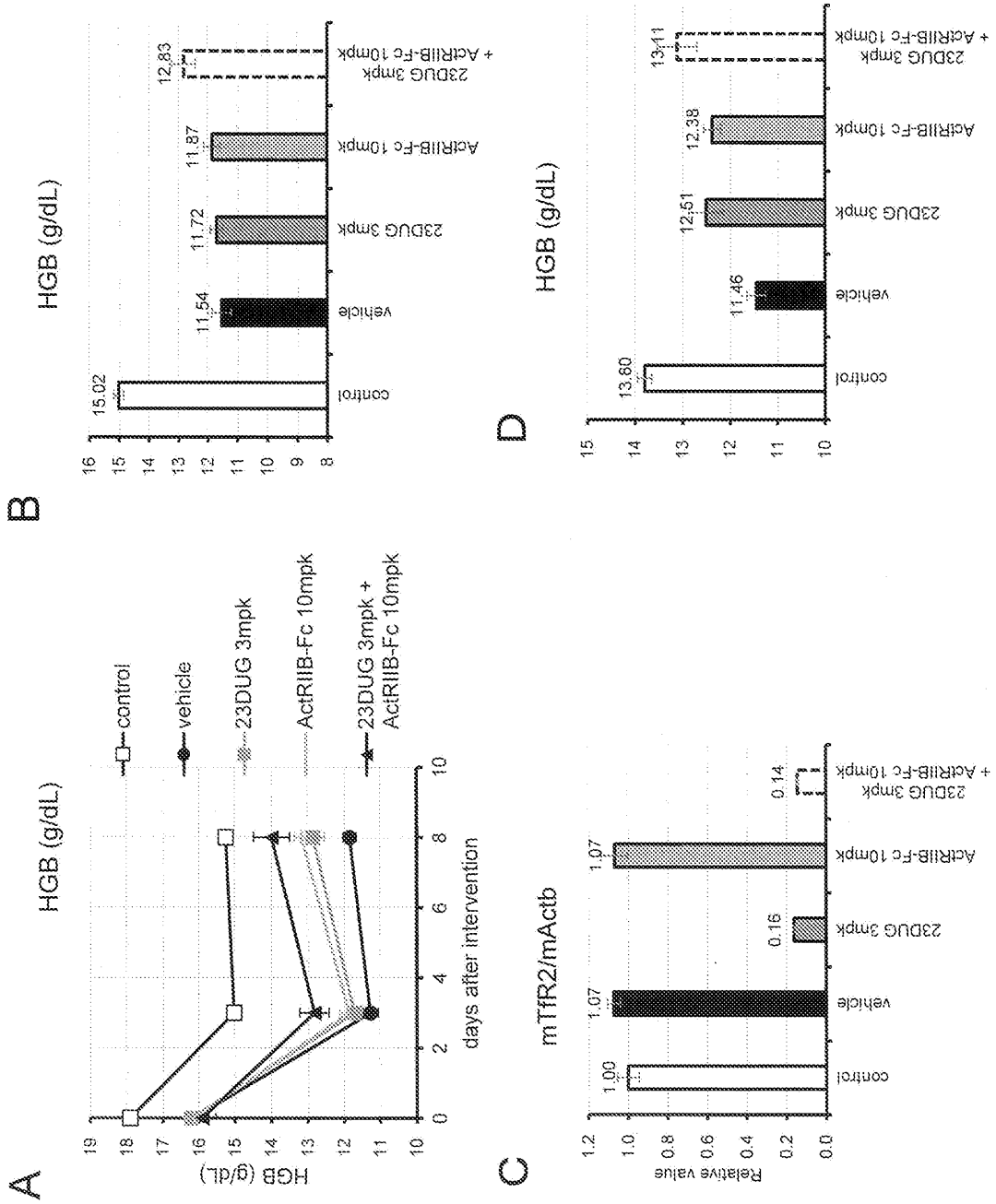
NNN-xxx.95DU



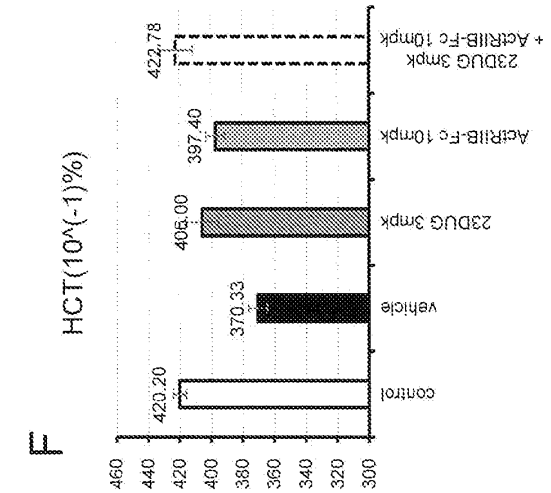
[図7]

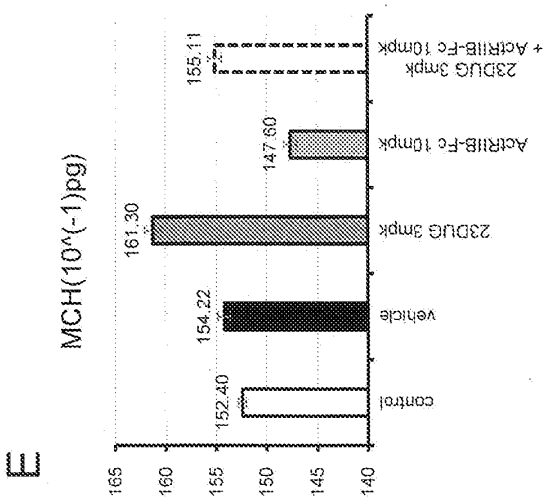

A
plasma Fe (ug/dL)
ug/dL
days after intervention
control
vehicle
0.5mpk
0.25mpk
B
plasma hepcidin (nM)
nM
days after intervention
control
vehicle
0.5mpk
0.25mpk
C
HGB (g/dL)
g/dL
days after intervention
vehicle
0.5mpk
0.25mpk
D
MCH(10^(-1)pg)
147.20
148.50
160.29
157.57
control
vehicle
0.5mpk
0.25mpk
E
mTfR2/mActB
relative value
1.00
0.90
0.28
0.40
control
vehicle
0.5mpk
0.25mpk
TfR2-siRNA
F
mHepcidin/mActB
relative value
1.00
2.14
0.51
1.72
control
vehicle
0.5mpk
0.25mpk
TfR2-siRNA

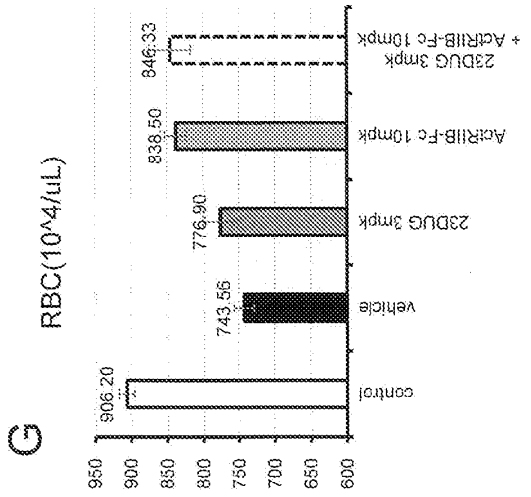
[図8-1]


A
HGB (g/dL)
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk
days after intervention
B
HGB (g/dL)
15.02
11.54
11.72
11.87
12.83
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk
C
mTfR2/mActb
Relative value
1.00
1.07
0.16
1.07
0.14
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk
D
HGB (g/dL)
13.60
11.46
12.51
12.38
13.11
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk

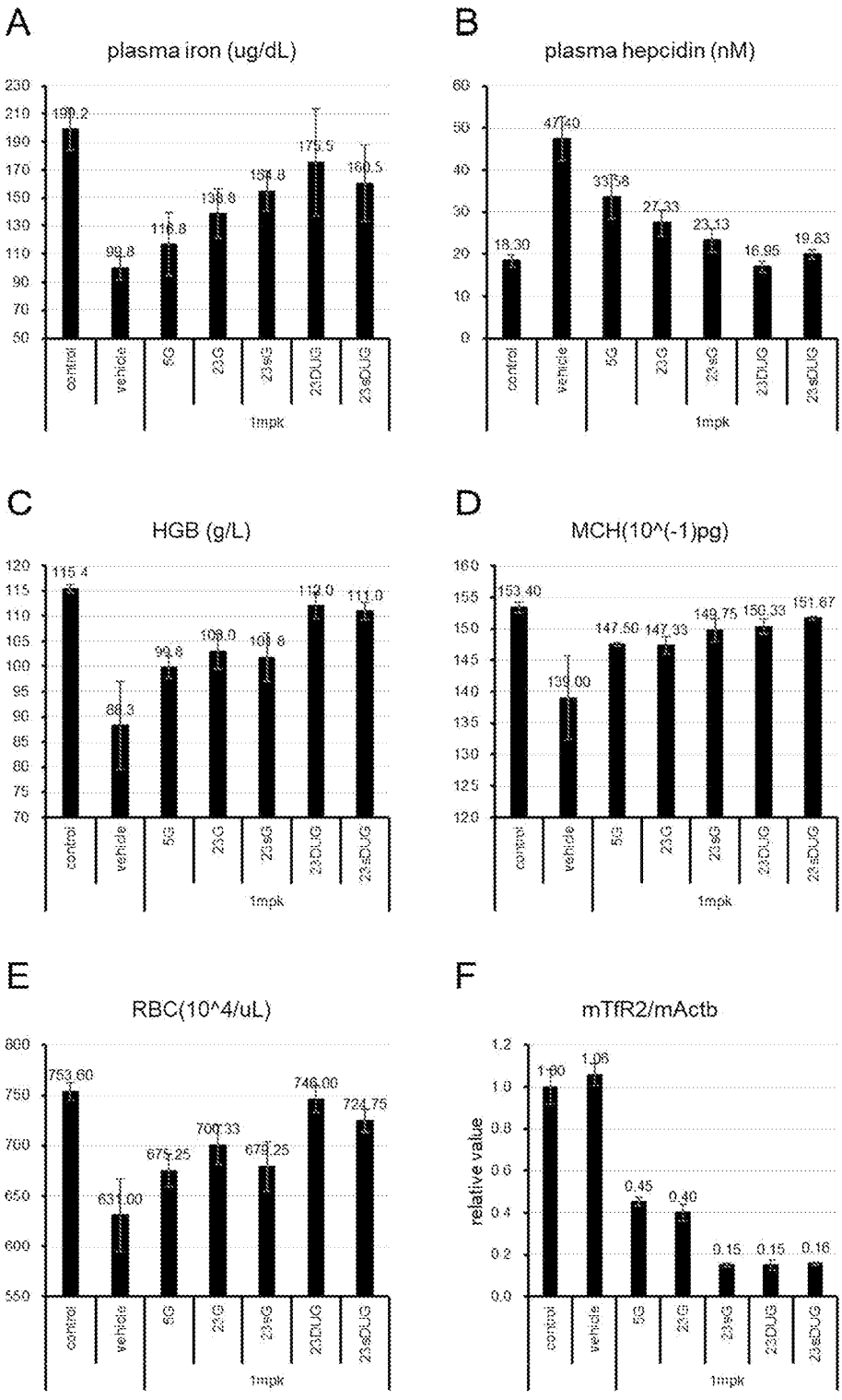
[図8-2]


F
HCT(10^(-1)%)
460
440
420
400
380
360
340
320
300
420.20
370.33
406.00
397.40
422.78
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk

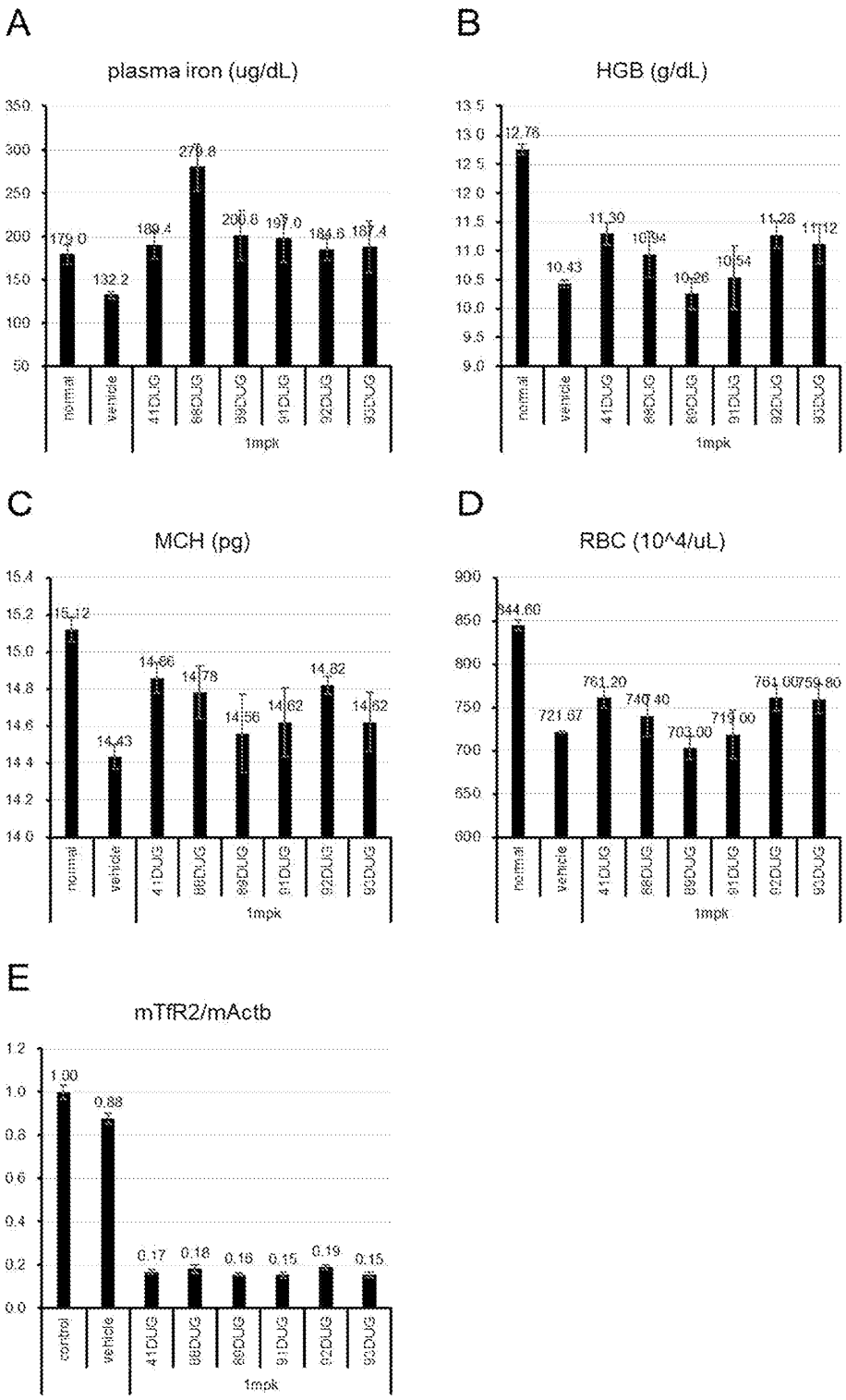

E
MCH(10^(-1)pg)
165
160
155
150
145
140
152.40
154.22
161.30
147.60
155.11
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk


G
RBC(10^4/uL)
950
900
850
800
750
700
650
600
906.20
743.56
776.90
838.50
846.33
control
vehicle
23DUG 3mpk
ActRIIB-Fc 10mpk
23DUG 3mpk + ActRIIB-Fc 10mpk

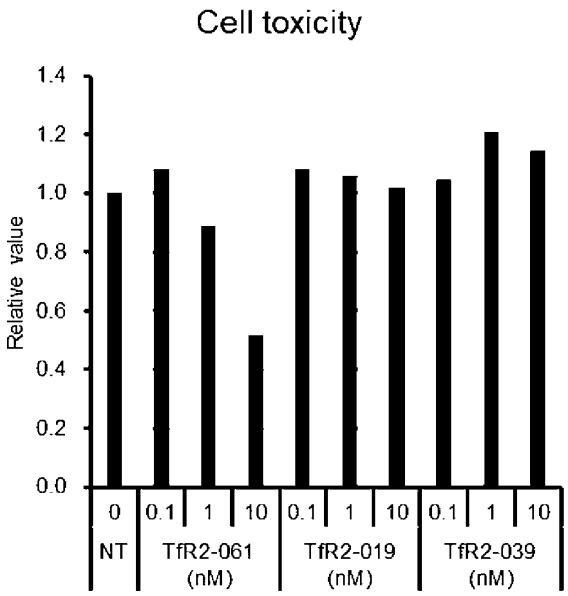
[図9]


A
plasma iron (ug/dL)
199.2
99.8
116.8
138.8
156.8
175.5
160.5
B
plasma hepcidin (nM)
18.30
47.40
33.58
27.33
23.13
16.95
19.83
C
HGB (g/L)
115.4
88.3
99.8
108.0
103.6
112.0
111.0
D
MCH(10^(-1)pg)
153.40
139.00
147.50
147.33
149.75
150.33
151.67
E
RBC(10^4/uL)
753.60
631.00
675.25
700.33
679.25
746.00
724.75
F
mTfR2/mActb
relative value
1.00
1.06
0.45
0.40
0.15
0.15
0.16
control
vehicle
5G
23G
23sG
23DUG
23sDUG
1mpk

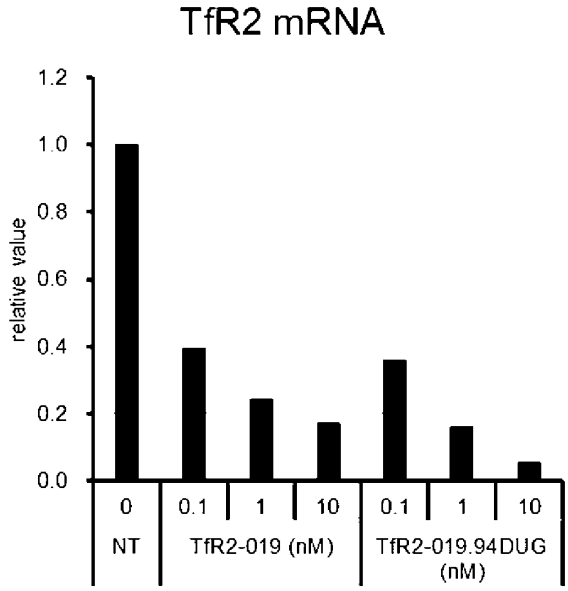
[図10]


A
plasma iron (ug/dL)
350
300
250
200
150
100
50
179.0
132.2
189.4
278.8
200.8
197.0
184.6
187.4
normal
vehicle
41DUG
86DUG
89DUG
91DUG
92DUG
93DUG
1mpk
B
HGB (g/dL)
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
12.76
10.43
11.30
10.94
10.26
10.54
11.28
11.12
C
MCH (pg)
15.4
15.2
15.0
14.8
14.6
14.4
14.2
14.0
15.12
14.43
14.86
14.78
14.56
14.62
14.82
14.62
D
RBC (10^4/uL)
900
850
800
750
700
650
600
844.60
721.67
761.20
740.40
703.00
719.00
761.00
759.80
E
mTfR2/mActb
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.00
0.88
0.17
0.18
0.16
0.15
0.19
0.15
control
vehicle
41DUG
86DUG
89DUG
91DUG
92DUG
93DUG
1mpk

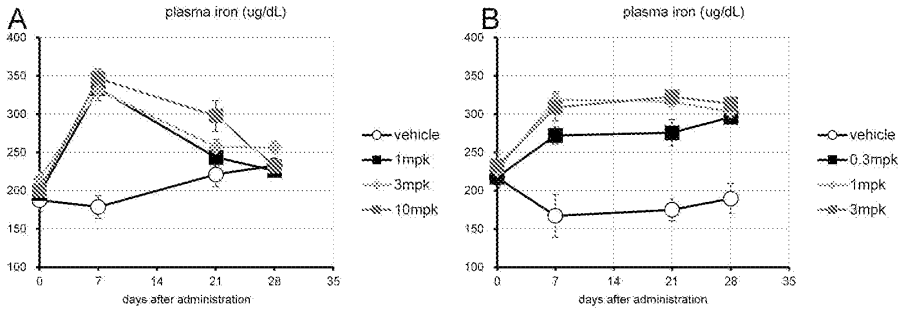
[図11]


Cell toxicity
Relative value
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
0.1
1
10
0.1
1
10
0.1
1
10
NT
TfR2-061 (nM)
TfR2-019 (nM)
TfR2-039 (nM)

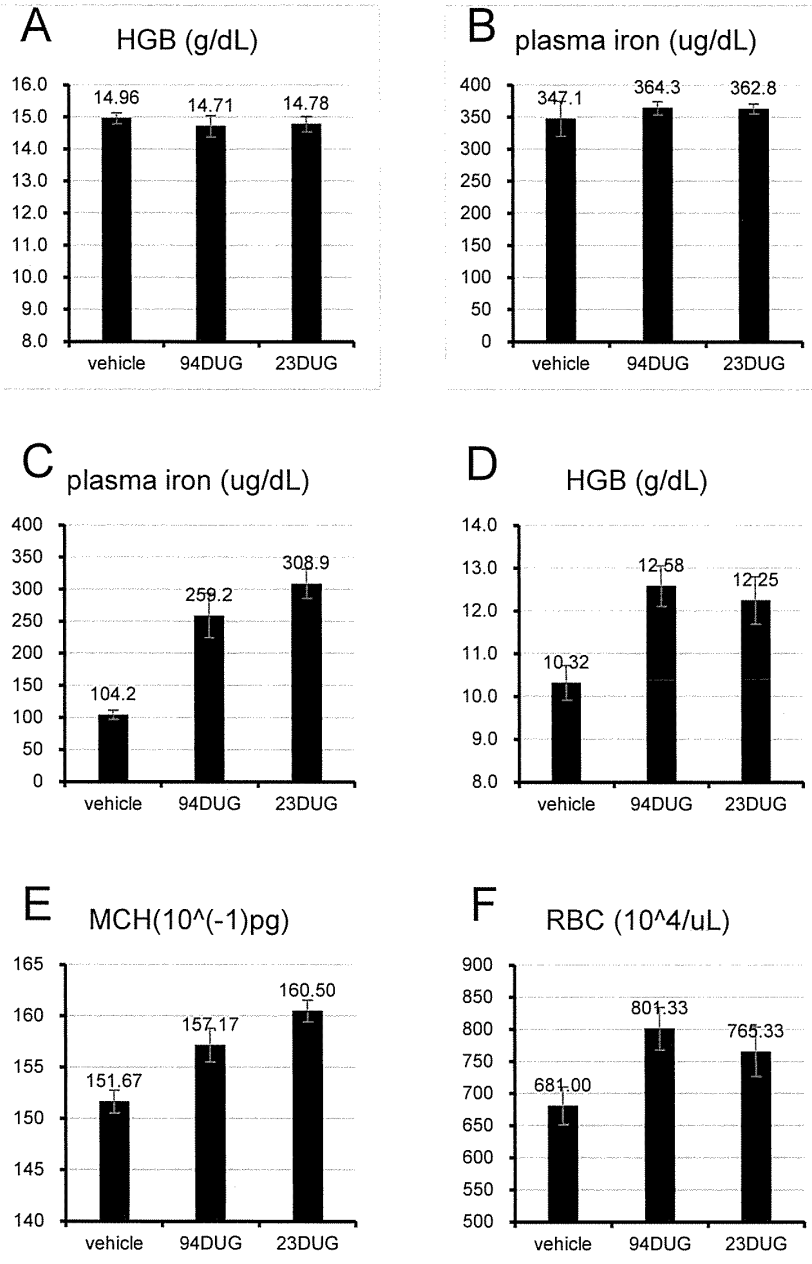
[図12]


TfR2 mRNA
relative value
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
0.1
1
10
0.1
1
10
NT
TfR2-019 (nM)
TfR2-019.94DUG (nM)

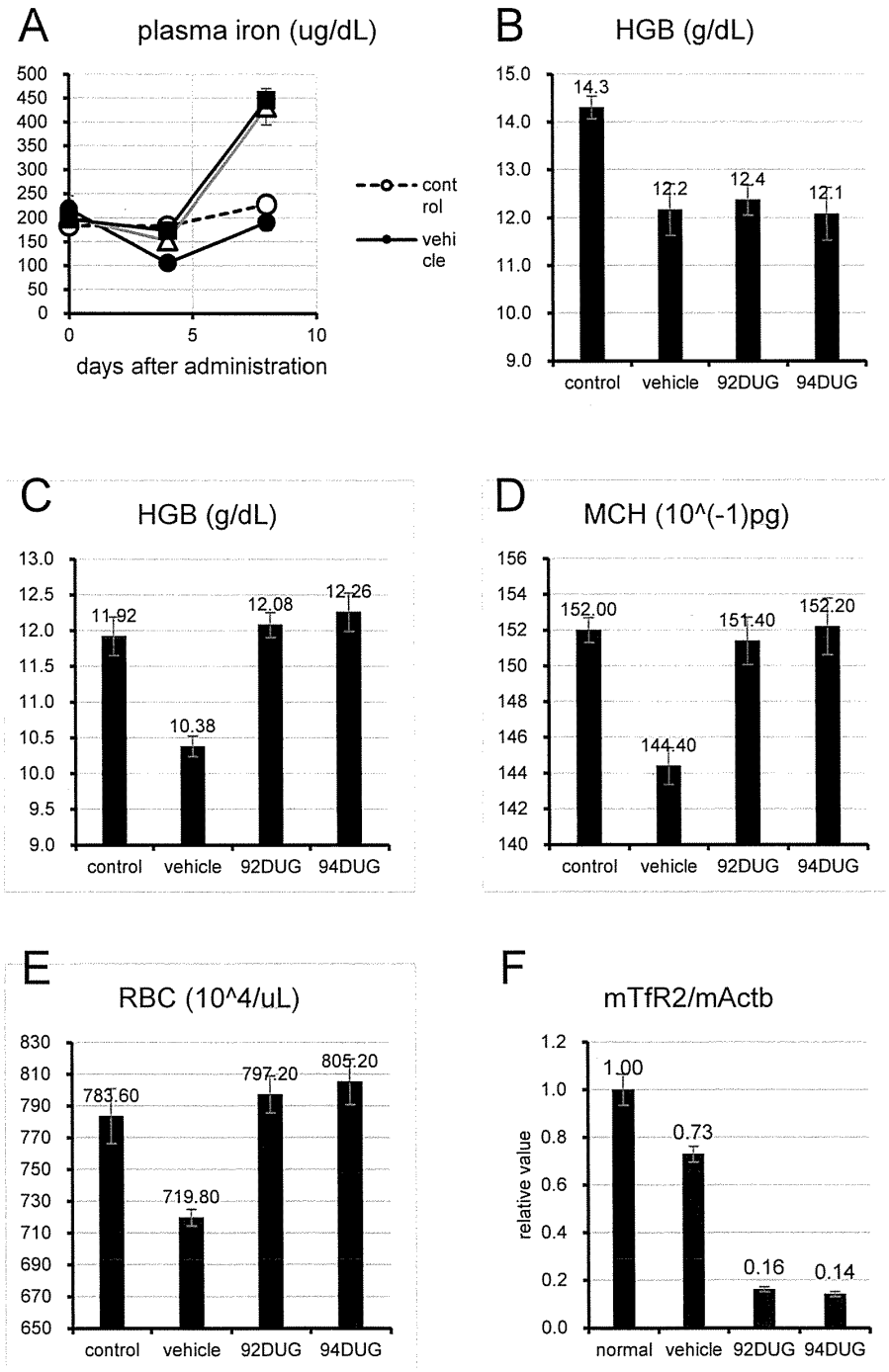
[図13]


A
plasma iron (ug/dL)
400
350
300
250
200
150
100
0
7
14
21
28
35
days after administration
vehicle
1mpk
3mpk
10mpk
B
plasma iron (ug/dL)
400
350
300
250
200
150
100
0
7
14
21
28
35
days after administration
vehicle
0.3mpk
1mpk
3mpk

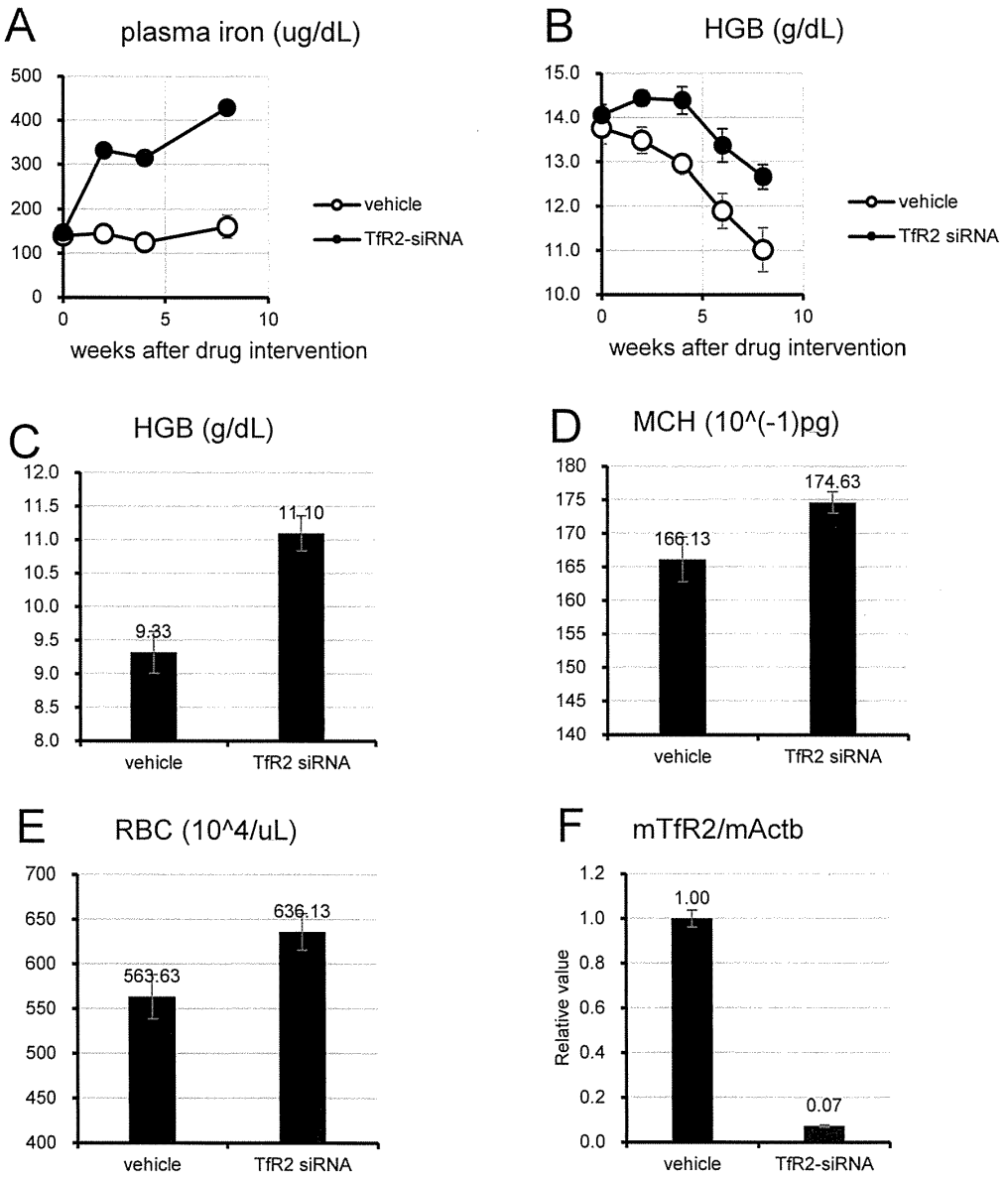
[図14]


A
HGB (g/dL)
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
14.96
14.71
14.78
vehicle
94DUG
23DUG
B
plasma iron (ug/dL)
400
350
300
250
200
150
100
50
0
347.1
364.3
362.8
vehicle
94DUG
23DUG
C
plasma iron (ug/dL)
400
350
300
250
200
150
100
50
0
104.2
259.2
308.9
vehicle
94DUG
23DUG
D
HGB (g/dL)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
10.32
12.58
12.25
vehicle
94DUG
23DUG
E
MCH(10^(-1)pg)
165
160
155
150
145
140
151.67
157.17
160.50
vehicle
94DUG
23DUG
F
RBC (10^4/uL)
900
850
800
750
700
650
600
550
500
681.00
801.33
765.33
vehicle
94DUG
23DUG

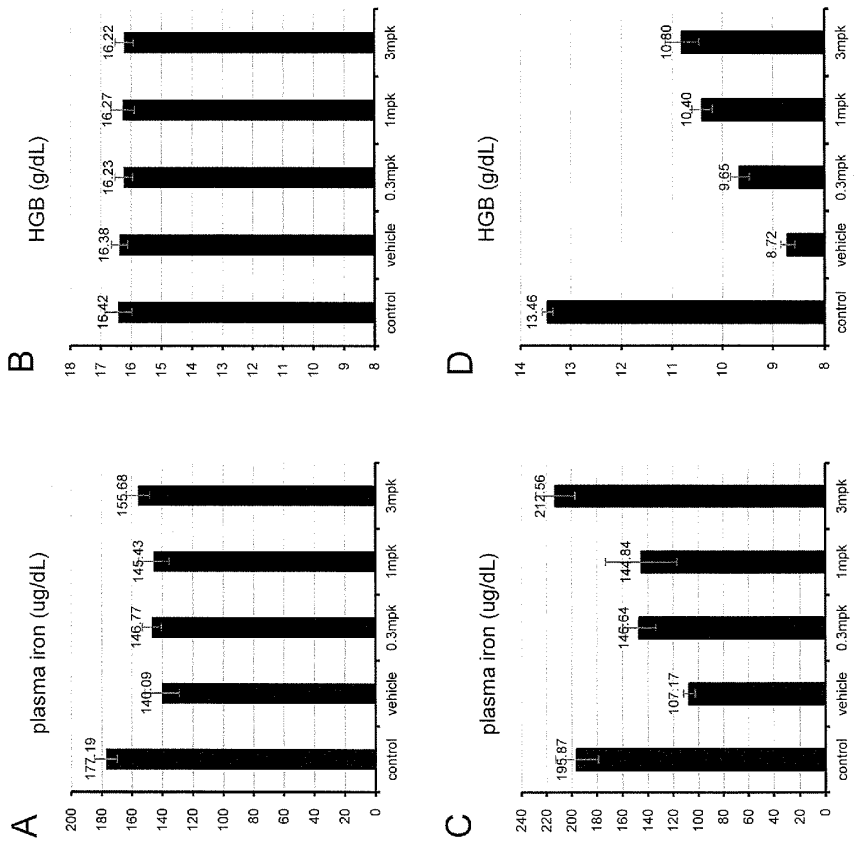
[図15]


A
plasma iron (ug/dL)
500
450
400
350
300
250
200
150
100
50
0
0
5
10
days after administration
control
vehicle
B
HGB (g/dL)
15.0
14.0
13.0
12.0
11.0
10.0
9.0
14.3
12.2
12.4
12.1
control
vehicle
92DUG
94DUG
C
HGB (g/dL)
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
11.92
10.38
12.08
12.26
control
vehicle
92DUG
94DUG
D
MCH (10^(-1)pg)
156
154
152
150
148
146
144
142
140
152.00
144.40
151.40
152.20
control
vehicle
92DUG
94DUG
E
RBC (10^4/uL)
830
810
790
770
750
730
710
690
670
650
783.60
719.80
797.20
805.20
control
vehicle
92DUG
94DUG
F
mTfR2/mActb
relative value
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.00
0.73
0.16
0.14
normal
vehicle
92DUG
94DUG

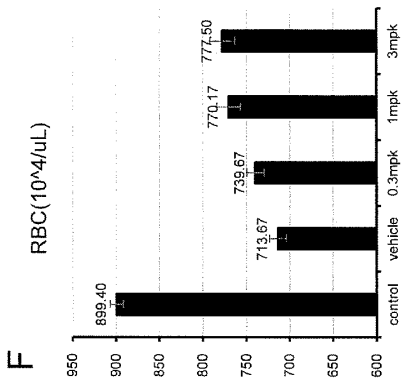
[図16]

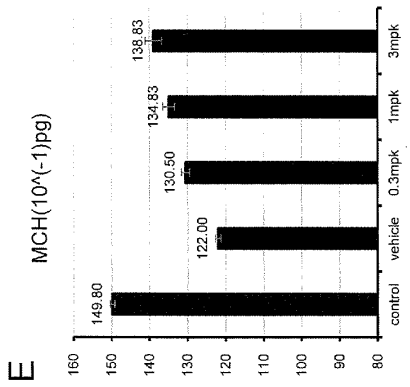

A
plasma iron (ug/dL)
500
400
300
200
100
0
0
5
10
weeks after drug intervention
vehicle
TfR2-siRNA
B
HGB (g/dL)
15.0
14.0
13.0
12.0
11.0
10.0
0
5
10
weeks after drug intervention
vehicle
TfR2 siRNA
C
HGB (g/dL)
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
9.33
11.10
vehicle
TfR2 siRNA
D
MCH (10^(-1)pg)
180
175
170
165
160
155
150
145
140
166.13
174.63
vehicle
TfR2 siRNA
E
RBC (10^4/uL)
700
650
600
550
500
450
400
563.63
636.13
vehicle
TfR2 siRNA
F
mTfR2/mActb
Relative value
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.00
0.07
vehicle
TfR2-siRNA

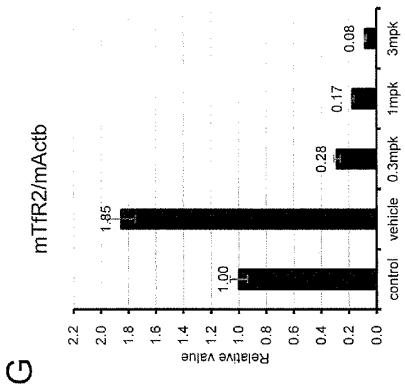
[図17-1]


A
plasma iron (ug/dL)
177.19
140.09
146.77
145.43
155.68
control
vehicle
0.3mpk
1mpk
3mpk
B
HGB (g/dL)
16.42
16.38
16.23
16.27
16.22
C
plasma iron (ug/dL)
195.87
107.17
145.64
144.84
212.56
D
HGB (g/dL)
13.46
8.72
9.65
10.40
10.80

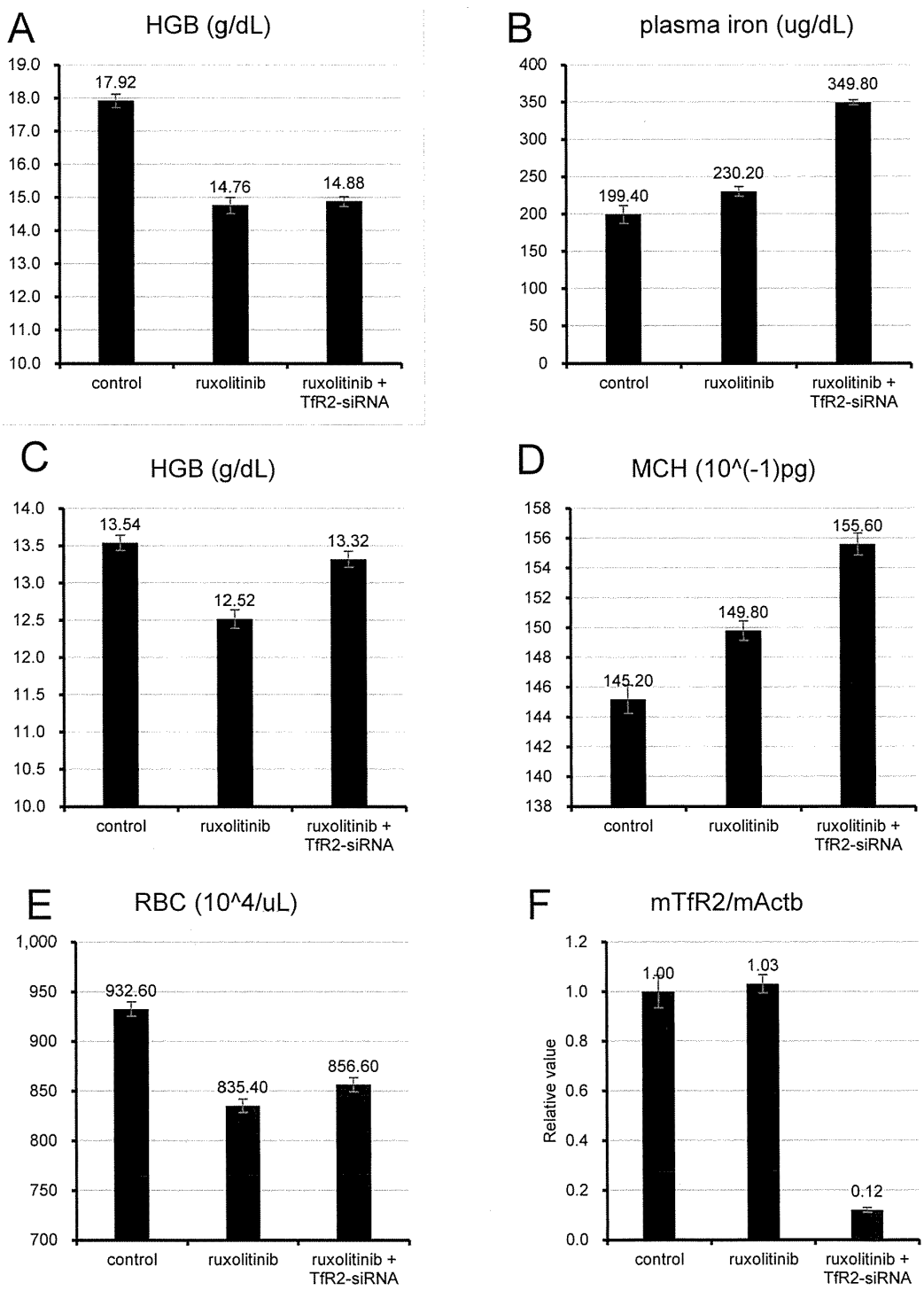
[図17-2]


F
RBC(10^4/uL)
950
900
850
800
750
700
650
600
899.40
713.67
739.67
770.17
777.50
control
vehicle
0.3mpk
1mpk
3mpk

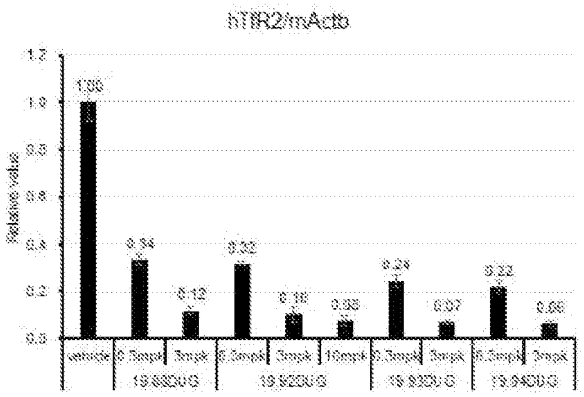

E
MCH(10^(-1)pg)
160
150
140
130
120
110
100
90
80
149.80
122.00
130.50
134.83
138.83
control
vehicle
0.3mpk
1mpk
3mpk


G
mTfR2/mActb
Relative value
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.00
1.85
0.28
0.17
0.08
control
vehicle
0.3mpk
1mpk
3mpk

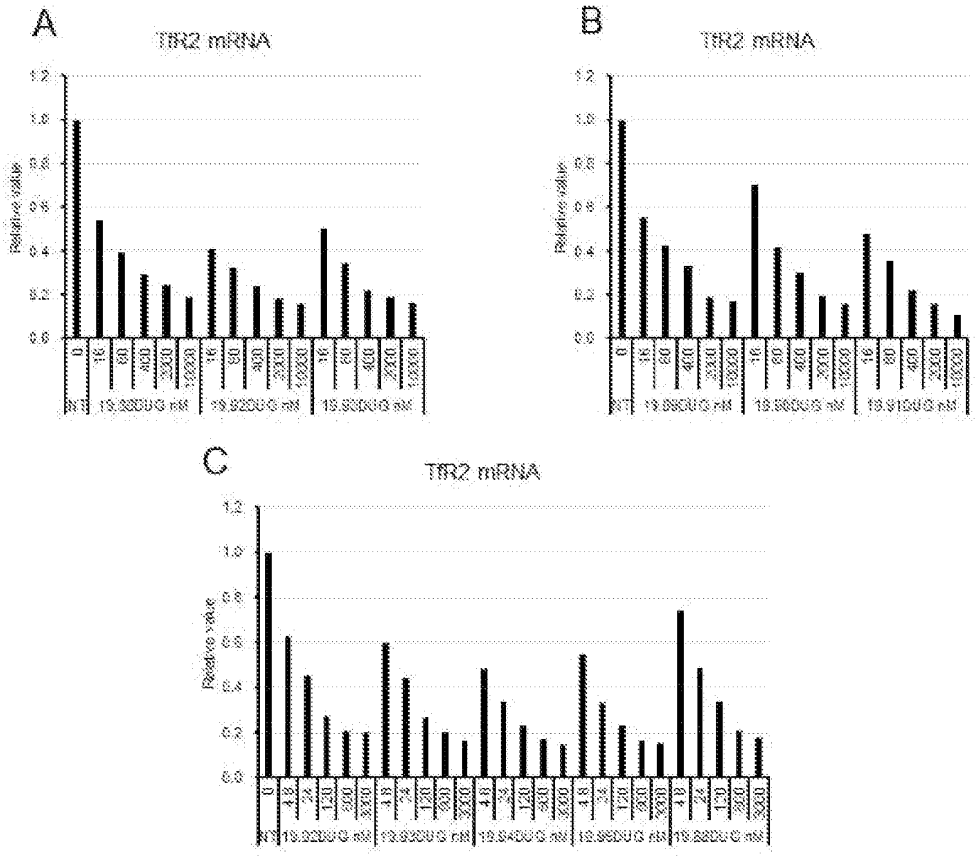
[図18]


A
HGB (g/dL)
19.0
18.0
17.0
16.0
15.0
14.0
13.0
12.0
11.0
10.0
17.92
14.76
14.88
control
ruxolitinib
ruxolitinib + TfR2-siRNA
B
plasma iron (ug/dL)
400
350
300
250
200
150
100
50
0
199.40
230.20
349.80
control
ruxolitinib
ruxolitinib + TfR2-siRNA
C
HGB (g/dL)
14.0
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
13.54
12.52
13.32
control
ruxolitinib
ruxolitinib + TfR2-siRNA
D
MCH (10^(-1)pg)
158
156
154
152
150
148
146
144
142
140
138
145.20
149.80
155.60
control
ruxolitinib
ruxolitinib + TfR2-siRNA
E
RBC (10^4/uL)
1,000
950
900
850
800
750
700
932.60
835.40
856.60
control
ruxolitinib
ruxolitinib + TfR2-siRNA
F
mTfR2/mActb
Relative value
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.00
1.03
0.12
control
ruxolitinib
ruxolitinib + TfR2-siRNA

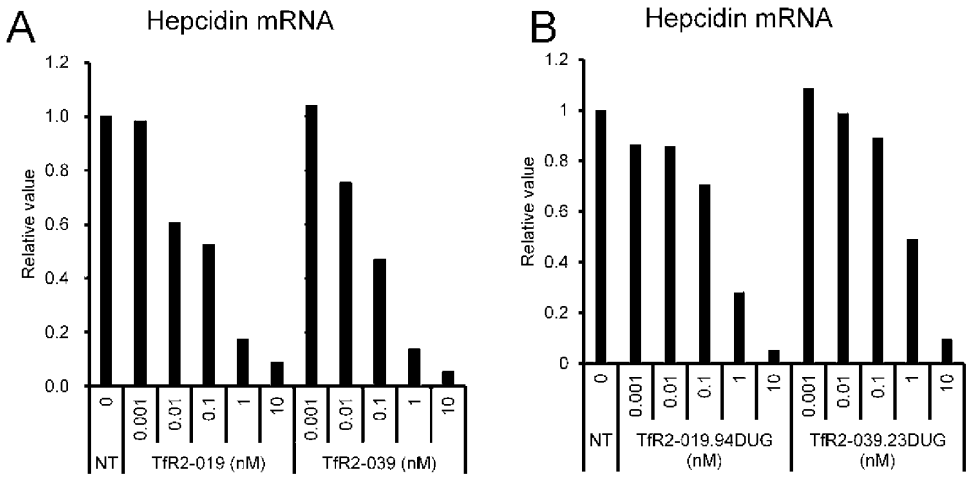
[図19]


hTlR2/mActb
Relative value
1.00
0.34
0.12
0.32
0.10
0.08
0.24
0.07
0.22
0.06
vehicle
3mpk
19.9820UG
19.9420UG

[図20]


A
TlR2 mRNA
B
TlR2 mRNA
C
TlR2 mRNA
Relative value

[図21]


A
Hepcidin mRNA
Relative value
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
0.001
0.01
0.1
1
10
0.001
0.01
0.1
1
10
NT
TfR2-019 (nM)
TfR2-039 (nM)
B
Hepcidin mRNA
Relative value
1.2
1
0.8
0.6
0.4
0.2
0
0
0.001
0.01
0.1
1
10
0.001
0.01
0.1
1
10
NT
TfR2-019.94DUG (nM)
TfR2-039.23DUG (nM)

[図22-1]

ｈＴｆＲ２　ｍＲＮＡのヌクレオチド配列（配列番号１）

aucgcugggg gacagccugc aggcuucagg aggggacaca agcauggagc ggcuuugggg 60
ucuauuccag agagcgcaac aacugucccc aagauccucu cagaccgucu accagcgugu 120
ggaaggcccc cggaaagggc accuggagga ggaagaggaa gacggggagg agggggcgga 180
gacauuggcc cacuucugcc ccauggagcu gaggggcccu gagccccugg gcucuagacc 240
caggcagcca aaccucauuc ccugggcggc agcaggacgg agggcugccc ccuaccuggu 300
ccugacggcc cugcugaucu ucacuggggc cuuccuacug ggcuacgucg ccuuccgagg 360
guccugccag gcgugcggag acucuguguu gguggucagu gaggauguca acuaugagcc 420
ugaccuggau uuccaccagg gcagacucua cuggagcgac cuccaggcca uguuccugca 480
guuccugggg gaggggcgcc uggaggacac caucaggcaa accagccuuc gggaacgggu 540
ggcaggcucg gccgggaugg ccgcucugac ucaggacauu cgcgcggcgc ucucccgcca 600
gaagcuggac cacgugugga ccgacacgca cuacgugggg cugcaauucc cggauccggc 660
ucaccccaac acccugcacu gggucgauga ggccgggaag gucggagagc agcugccgcu 720
ggaggacccu gacgucuacu gccccuacag cgccaucggc aacgucacgg gagagcuggu 780
guacgcccac uacgggcggc ccgaagaccu gcaggaccug cgggccaggg gcguggaucc 840
agugggccgc cugcugcugg ugcgcguggg ggugaucagc uucgcccaga aggugaccaa 900
ugcucaggac uucggggcuc aaggagugcu cauauaccca gagccagcgg acuucuccca 960
ggacccaccc aagccaagcc uguccagcca gcaggcagug uauggacaug ugcaccuggg 1020
aacuggagac cccuacacac cuggcuuccc uuccuucaau caaacccagu ucccuccagu 1080
ugcaucauca ggccuuccca gcaucccagc ccagcccauc agugcagaca uugccucccg 1140
ccugcugagg aagcucaaag gcccuguggc cccccaagaa uggcagggga gccuccuagg 1200
cucccccuau caccugggcc ccgggccacg acugcggcua guggucaaca aucacaggac 1260
cuccaccccc aucaacaaca ucuucggcug caucgaaggc cgcucagagc cagaucacua 1320
cguugucauc ggggcccaga gggaugcaug gggcccagga gcagcuaaau ccgcuguggg 1380
gacggcuaua cuccuggagc uggugcggac cuuuuccucc auggugagca acggcuuccg 1440
gccccgcaga agucuccucu ucaucagcug ggacgguggu gacuuuggaa gcgugggcuc 1500
cacggagugg cuagagggcu accucagcgu gcugcaccuc aaagccguag uguacgugag 1560
ccuggacaac gcagugcugg gggaugacaa guuucaugcc aagaccagcc cccuucugac 1620
aagucucauu gagaguguce ugaagcaggu ggauucuccc aaccacagug ggcagacucu 1680
cuaugaacag gugguguuca ccaaucccag cugggaugcu gaggugaucc ggccccuacc 1740
cauggacagc agugccuauu ccuucacggc cuuuguggga gucccugccg ucgaguucuc 1800

[図22-2]

cuuuauggag gacgaccagg ccuacccauu ccugcacaca aaggaggaca cuuaugagaa 1860

ccugcauaag gugcugcaag gccgccugcc cgccguggcc caggccgugg cccagcucgc 1920

agggcagcuc cucauccggc ucagccacga ucgccugcug ccccucgacu ucggccgcua 1980

cggggacguc guccucaggc acaucgggaa ccucaacgag uucucugggg accucaaggc 2040

ccgcgggcug acccugcagu ggguguacuc ggcgcggggg gacuacaucc gggcggcgga 2100

aaagcugcgg caggagaucu acagcucgga ggagagagac gagcgacuga cacgcaugua 2160

caacgugcgc auaaugcggg uggaguucua cuuccuuucc caguacgugu cgccagccga 2220

cucccguuc cgccacaucu ucaugggccg uggagaccac acgcugggcg cccugcugga 2280

ccaccugcgg cugcugcgcu ccaacagcuc cgggaccccc ggggccaccu ccuccacugg 2340

cuuccaggag agccguuucc ggcgucagcu agcccugcuc accuggacgc ugcaaggggc 2400

agccaaugcg cuuagcgggg augucuggaa cauugauaac aacuucugag gcccuggga 2460

uccucacauc cccgucccc agucaagagc uccucugcuc cucgcuugaa ugauucaggg 2520

ucagggaggu ggcucagagu ccaccucuca uugcugauca auuucucauu accccuacac 2580

aucucuccac ggagcccaga ccccagcaca gauauccaca caccccagcc cugcagugua 2640

gcugacccua augugacggu cauacugucg guuaaucaga gaguagcauc ccuucaauca 2700

cagccccuuc cccuuucugg gguccuccau accuagagac cacucuggga gguuugcuag 2760

gcccugggac cuggccagcu cuguuagugg gagagaucgc uggcaccaua gccuuauggc 2820

caacaggugg ucugugguga aaggggcgug gaguuucaau aucaauaaac caccugauau 2880

caauaa 2886