B型肝炎創薬実用化等研究事業

研究課題名：
HBV cccDNAの制御と排除を目指す新規免疫治療薬の開発

研究代表者
金沢大学
医薬保健研究域医学系
金子周一

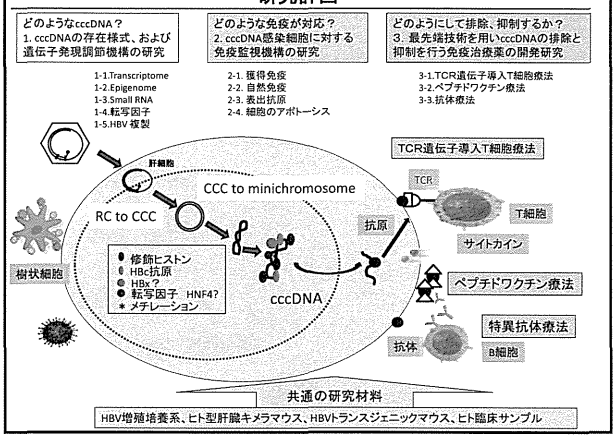
研究の目的

目的：
免疫によってHBV感染を排除あるいは制御する治療法を開発する。

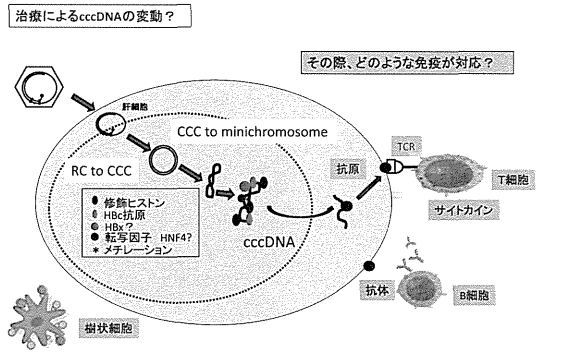
背景：

免疫を用いた治療法の開発はめざましく、がん領域ではすでに、
がん治療を変える画期的な臨床成績が示され始めた。
他の疾病領域でも免疫を用いた治療法の開発が進められている。

研究計画

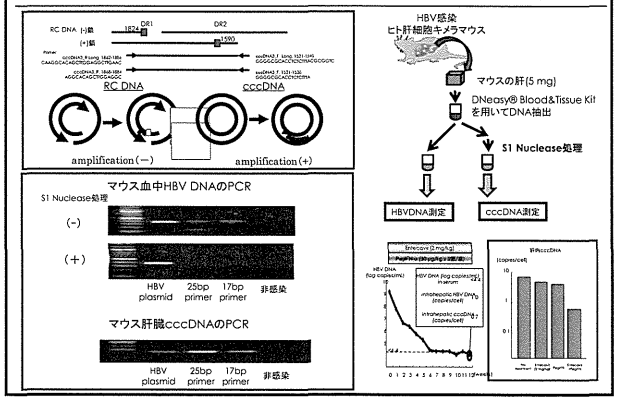


どのようなcccDNAの存在様式に対し、どのような免疫が対応してHBVが制御されているか

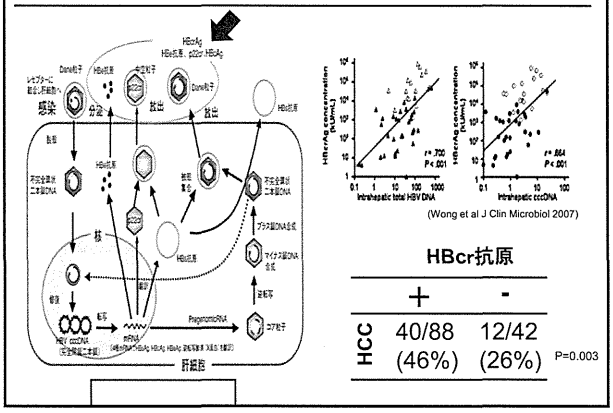


報告されているcccDNAの測定法はfalse positiveが問題であったが、primer調整およびS1 Nuclease処理によって肝内HBV cccDNAを特異的に測定するシステムを構築した

分担研究者：今村道雄



HBcr抗原量はHBV複製およびcccDNA量と相関し、発がんとの関連も示唆されている



(Wong et al J Clin Microbiol 2007)

HCC	HBcr抗原 +	HBcr抗原 -
	40/88 (46%)	12/42 (26%)

P=0.003

核酸アナログ投与によるHBcr抗原量の変化と、発現遺伝子プロファイルの変化

核酸アナログ平均5年

↑ 肝生検① ⟺ 肝生検② ↑

遺伝子発現の比較

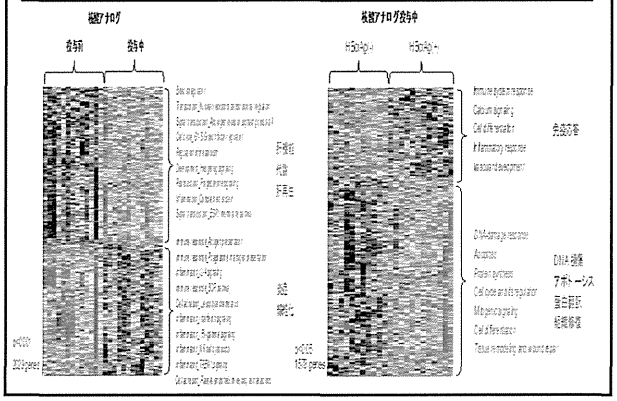
HBcrAg(+)

⇕

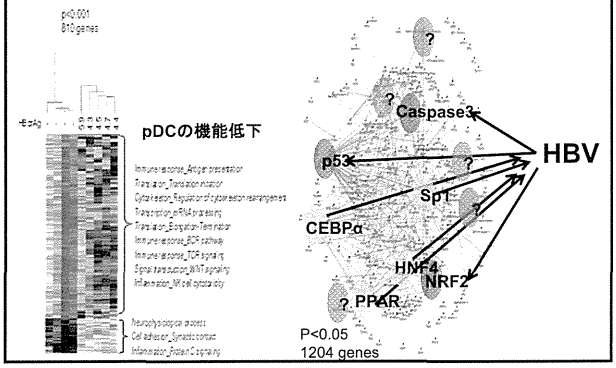
HBcrAg(-)

Age	Sex	F	A	HBV-DNA	e/o	HBV genotype	HBcrAg
63	F	0~1	0~1	-	+	C	-
65	F	0~1	0~1	-	+	C	-
31	M	0~1	1	2.1	+	B	-
68	M	0~1	1	<2.1(+)	+	C	-
54	F	0~1	0~1	<2.1(+)	+	B	-
65	M	0	0	-	+	B	-
59	M	1	1	-	+	C	-
66	M	3~4	0~1	<2.1(+)	+	判定保留	-
49	M	1	1	-	+	C	-
66	M	3	0	-	+	C	-
63	M	1	1	-	+	判定保留	-
64	M	1	1	<2.1(+)	-	C	47
65	M	4	1	<2.1(+)	+	C	43
63	F	4	1	<2.1(+)	+	C	35
59	F	4	1	<2.1(+)	+	C	4
38	M	1	0~1	<2.1(+)	+	C	47
46	F	1~2	0	<2.1(+)	+	C	43
64	M	1	0~1	<2.1(+)	+	C	4
59	M	3	1	<2.1(+)	+	C	33
37	F	0	1	-	+	C	43
65	M	3~4	1	<2.1(+)	+	C	34
56	M	3~4	1	<2.1(+)	+	C	35
66	M	3	1	<2.1(+)	+	C	33

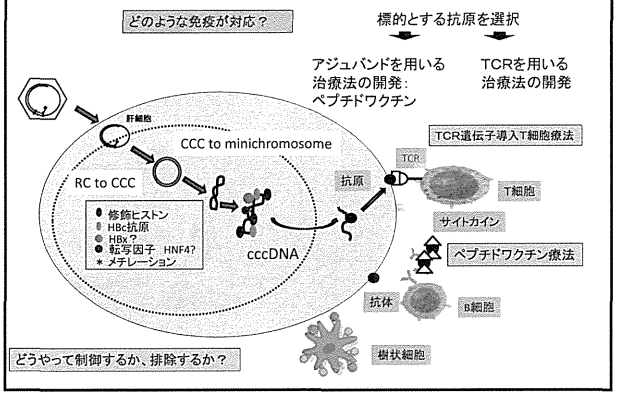
核酸アナログ投与によるHBcr抗原量の変化と、発現遺伝子プロファイルの変化



核酸投与によってHBcr抗原が残っている症例では免疫能、特にpDCの機能低下が認められた細胞内ではHNF4やSP1をはじめとするHBVプロモーターを活性化する転写因子の発現増加が見られ、HBVの複製を支持する環境にあると考えられた

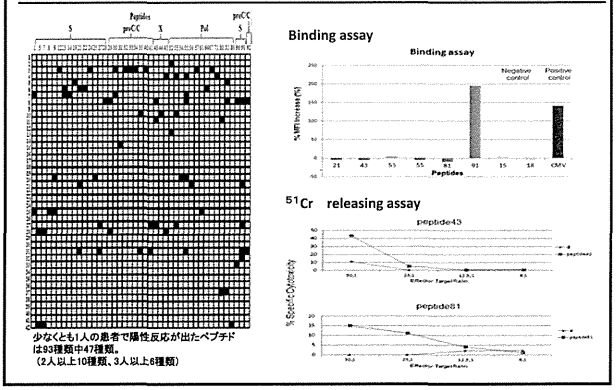


どのような免疫が対応してHBVが制御されているか、どのようにして排除できるか



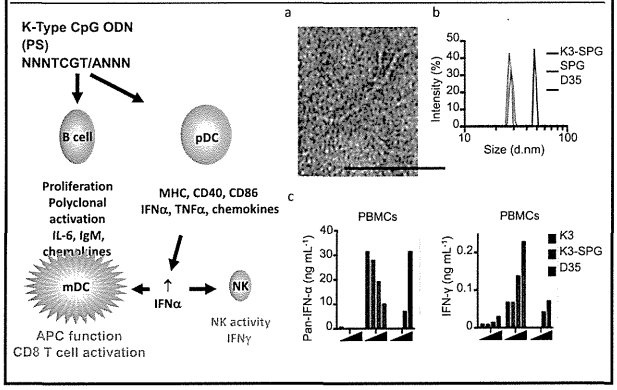
93種類のペプチドを作製し、42例の患者を対象に反応を確認し候補抗原として6種類を選択した、さらにBinding assay, ^{51}Cr release assayを実施し候補を選択している

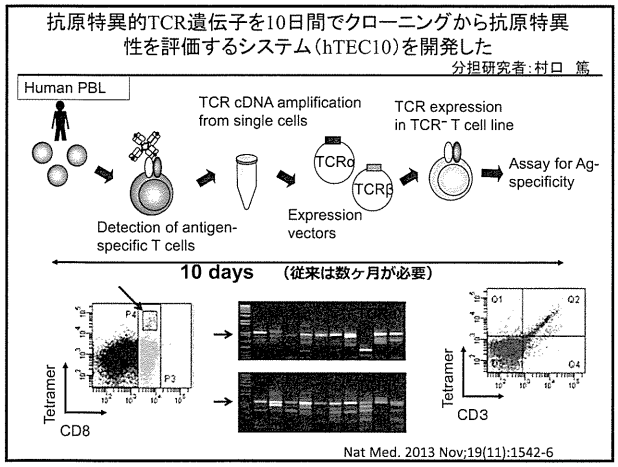
分担研究者：水腰英四朗

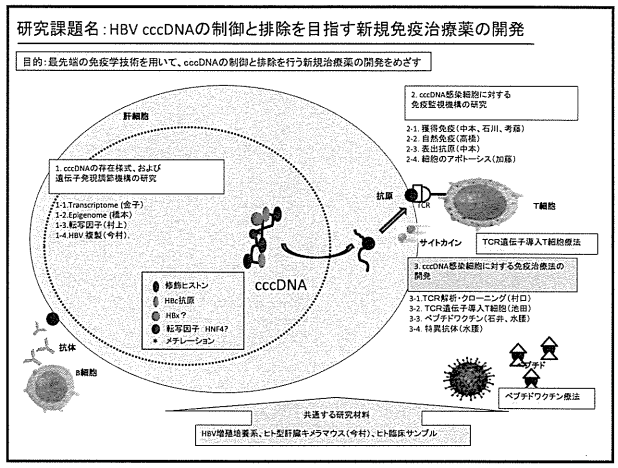


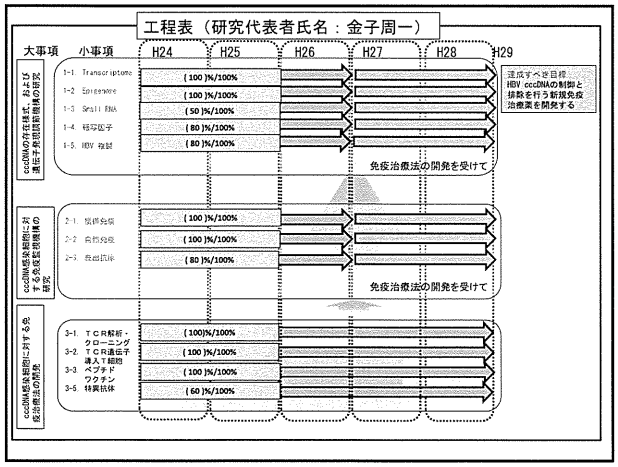
免疫能を高めるアジュバンドとしてTLR9リガンドであるCpG ODNを開発している:pDCに働き、高いIFN誘導能を示すアジュバンドが得られた

分担研究者：石井健









利益相反について

利益相反の有無等(平成25年度)

ア 利益相反の有無　　有・無(いずれかを記載)
イ 利益相反がある場合には具体的内容(以下に記載)

ア 利益相反 無

他の研究班への参加状況

研究代表者が、「肝炎等克服緊急対策研究事業」または「難病・がん等の疾患分野の医療の実用化研究事業(肝炎関係研究分野)」研究班の研究代表者として参加しているか(ア又はイに記載)

ア 上記研究事業の研究班の研究代表者として参加していない。
イ 上記研究事業の研究班の研究代表者として参加している。
(以下①、②を記載)
①(研究班名)「○○○○研究班」(研究代表者名:○○○○)
② 他の研究班で担当している研究と、今回申請している研究の違い(研究内容が重複していないことを具体的に説明)

イ
①「C型肝炎から発がんにいたる病態進展の解明とその制御に関する研究」
(研究代表者名:金子周一)
②C型肝炎からの肝がん発症にいたる病態を分子および細胞レベルで解明しその病態に対する治療法の開発をめざした研究であり、本研究課題とは研究内容が重複していません。

合同研究班会議開催状況

他の研究班と合同での研究班会議開催状況(平成25年度)

ア 他の研究班と合同で研究班会議を開催していない。
イ 他の研究班と合同で研究班会議を開催している。
(開催している場合は、①開催日、②他の研究班の名称、③他の研究班の研究代表者名を記載してください)

イ
①平成25年8月22日、平成26年1月10日
② B型肝炎ウイルスの持続感染を再現する効率的な培養細胞評価系の開発に関する研究
③田中靖人

平成25年度 B型肝炎創薬実用化等研究事業『成果概要』

研究課題：人工キメラ遺伝子と肝臓特異的な輸送担体の開発を基盤とした肝臓内HBVDNA不活化を目指した新規治療法の開発

課題番号　：H24-B創-肝炎-一般-011
予定期間　：H24年度からH28年度まで
研究代表者　：溝上　雅史
所属研究機関：国立国際医療研究センター
所属部局　：肝炎・免疫研究センター
職名　：肝炎・免疫研究センター長
年次別研究費(交付決定額)：1年目 200,000,000円　2年目 200,000,000円

Ⅰ．研究の意義

(1)B型肝炎に対する従来の医薬品や治療法では、肝細胞核内のHBVDNAに直接作用してHBV複製を根本的に停止させることが出来なかった。
(2)ウイルスベクターを用いず、ホストゲノムへの偶発的な挿入がなく、安全かつ特異的に肝臓へ治療物質を輸送する手段の開発が望まれている。
(3)HBV感染が成立すると、その完全な排除は不可能でHBVが再活性化するリスクを一生負うことになり、特に免疫抑制を伴う疾患や治療では、HBV感染が障害となることがある。

Ⅱ．研究の目的、期待される成果

(1) HBV複製の鋳型となるcccDNAとインテグレーションされたHBVDNAに対して，配列特異的に作用する人工キメラ遺伝子（Zinc Finger Nucelase（ZFN）、TAL Effector Nucleases（TALENs）、CRISPR/Cas9）を設計・選抜することでHBVDNA切断と不活化を目的とする．
(2)新規のドラッグデリバリーシステム（DDS）として、高分子ポリマーを応用した自己会合型のナノ粒子を設計し、その粒子内に核酸医薬品を封入する。さらに、肝臓特異的な輸送能を持たせる。
(3)上記により、細胞核内のHBVDNAを不活化し、HBVの持続感染を根本的な手段により解決へ導く。
(4)肝臓特異的に安全な輸送ができるDDSは、既存の薬物輸送へも応用可能であり汎用性がある。

Ⅲ．2年間の研究成果

※この期間にどのような成果があったか、研究代表者、研究分担者毎に、できるだけわかりやすく具体的に記述してください。

・研究代表者

(1)HBVを恒常発現する細胞でZFNを作用させ、切断活性とウイルス減少を確認した。
(2)初代培養肝細胞へのHBV感染系の確立をおこない、ZFNの効果を確認した。

・研究分担者(片岡　一則)

(1)肝臓へ効率的にmRNAを送達するためのナノミセル輸送担体の開発に成功した。

(2)ナノミセル型mRNA輸送担体を用いて、ほぼすべての肝細胞に効率的にタンパク質発現させた。
(3)ナノミセル導入後の肝組織傷害や炎症反応は一過性で軽度であり、安全性が確認された。

・研究分担者(中西　真)

(1)非常に低レベルのDNA二重鎖切断でも、細胞周期に応じて効率的に細胞老化が誘導された。
(2)人工キメラ遺伝子の一過性発現では細胞老化は認めなかったが、長期間での影響は解析中である。

・研究分担者(武冨　紹信)

(1)肝細胞癌初回切除症例の切除肝組織からの肝細胞の初代培養条件の検討を行った。
(2)肝細胞癌初回切除症例の切除肝組織、血液集積と管理、臨床経過の集積と予後解析を実施した。

・研究分担者(田中　榮司)

(1) 自然経過および抗ウイルス療法時のHBs抗原量とHBcr抗原量の推移を検討した。
(2) 血中HBV RNA量の測定方法を確立しその臨床的意義を検討した。

・研究分担者(星野　真一)

(1)人工合成mRNAの細胞内での分解経路を解明し、mRNAを安定化することに成功した。
(2)人工mRNAの末端修飾と翻訳因子の繋留により、mRNAの翻訳を効率化することに成功した。

・研究分担者(杉山　真也)

(1)ZFNの切断活性をGFPで可視化するシステムを確立した。
(2)人工キメラ遺伝子のオフターゲット効果を検証するための全ゲノム解析を実施した。

・研究分担者(福原　崇介)

(1)HBVゲノムのうち、保存されている領域を標的としたCRISPR/Cas9システムを確立した。
(2)In vitroモデルにおいて抗HBV活性を認めた。

・研究分担者(安井　文彦)

(1)HBV DNA選択的なTALENを3種類、CRISPR/Cas9を4種設計し、効果的な切断活性を確認した。

Ⅳ. 平成26～28年度の課題

(1)各人工キメラ遺伝子の最適化とそれらのin vivo、ex vivoでの活性確認
(2)ナノDDSのin vivo、ex vivoでの効果と安全性の検証
(3)DNA切断活性が細胞へ与える影響のin vivoモデルでの評価
(4)各人工キメラ遺伝子へのmRNA安定手法の応用と抗HBV活性の確認
(5)外科材料を用いたex vivoでのHBV感染系の最適化と株化
(6)臨床応用時のHBVDNA切断効果の評価手法の血液マーカーでの検討

Ⅴ. 行政施策への貢献の可能性

(1)B型肝炎患者は病気の「完治」を希望しているが、HBVの性質上、感染成立後は完全に排除できないため、ウイルスの抑制が今の限界である。しかしながら、細胞核内のHBVDNAを不活化する本研究を進めることで、患者の望む完治に極めて近い治療を提供できると考えられる。
(2)本研究で開発を行うDDSは、肝臓特異的に輸送できるナノデバイスの完成を目指しており、他へ様々な応用が可能なため、既存または将来開発される薬剤の輸送手段を改善でき、汎用性がある。
(3)免疫抑制を伴う移植や分子標的治療で誘発されるHBV再活性化リスクへの根本的な対策となりうる。

Ⅵ. 本研究の成果（発表論文・ガイドライン・マニュアル等）

※本研究費において行った研究に対するもののみを記載してください。

※研究代表者、研究分担者、研究協力者ごとに、発表論文名・学協会誌名・発表年（西暦）、
知的財産権の取得及び申請状況、ガイドライン名・作成主体・策定年月日等を記載して下さい。

※執筆者全員を明記し、当該研究者名に下線を引いてください。

研究代表者

(1) Ito K, Yotsuyanagi H, Yatsuhashi H, Karino Y, Takikawa Y, Saito T, Arase Y, Imazeki F, Kurosaki M, Umemura T, Ichida T, Toyoda H, Yoneda M, Mita E, Yamamoto K, Michitaka K, Maeshiro T, Tanuma J, Tanaka Y, Sugiyama M, Murata K, Masaki N, **Mizokami M**. Risk factors for long-term persistence of serum hepatitis B surface antigen following acute hepatitis B virus infection in Japanese adults. ***Hepatology*** 2013 Jul.29

研究分担者（片岡　一則）

(2) Uchida S, Itaka K, Uchida H, Hayakawa K, Ogata T, Ishii T, Fukushima S, Osada K, **Kataoka K**. In vivo messenger RNA introduction into the central nervous system
using polyplex nanomicelle. ***PLoS One***. 2013;8(2):e56220.

研究分担者（中西　真）

(3) Nishiyama A, Yamaguchi L, Sharif J, Johmura Y, Kawamura T, Nakanishi K, Shimamura S, Arita K, Kodama T, Ishikawa F, Koseki H, **Nakanishi M.** Uhrf1-dependent H3K23 ubiquitylation couples maintenance DNA methylation and replication. ***Nature***. 12488.2013

(4) Shimada M, **Nakanishi M.** Response to DNA damage: why do we need to focus on protein phosphatases? ***Front Oncol***. ;3:8.2013

(5) Hamajima N, Johmura Y, Suzuki S, **Nakanishi M,** Saitoh S Increased Protein Stability of CDKN1C Causes a Gain-of-Function Phenotype in Patients with IMAGe Syndrome. ***PLoS One***. Sep 30;8(9):e75137.2013

(6) Nishigaki M, Kawada Y, Misaki T, Murata K, Goshima T, Hirokawa T, Yamada C, Shimada M, **Nakanishi M.** Mitotic phosphorylation of MPP8 by cyclin-dependent kinases regulates chromatin dissociation. ***Biochem Biophys Res Commun.*** 432(4):654-9.2013

(7) Aoki Y, Sakogawa K, Hihara J, Emi M, Hamai Y, Kono K, Shi L, Sun J, Kitao H, Ikura T, Niida H, **Nakanishi M,** Okada M, Tashiro S Involvement of ribonucleotide reductase-M1 in 5-fluorouracil-induced DNA damage in esophageal cancer cell lines. ***Int J Oncol.***;42(6):1951-60.2013

研究分担者（田中　榮司）

(8) Morita S, Matsumoto A, Umemura T, Shibata S, Kamijo N, Ichikawa Y, Kimura T, Joshita S, Komatsu M, Yoshizawa K, **Tanaka E**. Characteristics and prediction of hepatitis B e-antigen negative hepatitis following seroconversion in patients with chronic hepatitis B. ***Hepatol Res*** (in press)

(9) Hagiwara S, Kudo M, Osaki Y, Matsuo H, Inuzuka T, Matsumoto A, **Tanaka E**, Sakurai T, Ueshima K, Inoue T, Yada N, Nishida N. Impact of peginterferon alpha-2b and entecavir hydrate combination therapy on persistent viral suppression in patients with chronic hepatitis B. ***J Med Virol*** 2013; 85: 987-995.

研究分担者（星野　真一）

(10) Saito, S., Hosoda, N., **Hoshino, S**. Hbs1-Dom34 functions in non-stop mRNA decay (NSD) in mammalian cells. ***J Biol Chem*** 2013; 288, 17832-17843.

(11) Ogami,K., Cho, R., **Hoshino, S**. Molecuar cloning and characterization of a novel isoform of the non-canonical poly(A) polymerase PAPD7. Biochem Biophys Res Commun. 2013; 432, 135-140.

(12) Ogami, K., Hosoda, N., Funakoshi, N., **Hoshino, S**. Anti prolifetative protein Tob directly regulates c-myc proto-oncogene expression through cytoplasmic polyadenylation element-binding protein CPEB. ***Oncogene*** (in press).

研究分担者（杉山　真也）

(13) Trinks J, **Sugiyama M**, Tanaka Y, Kurbanov F, Benetucci J, Giménez E,Weissenbacher MC, Mizokami M, Oubiña JR. In vitro replication competence of a hepatitis B genotype D/A recombinant virus: dissimilar biological behavior regarding its parental genotypes. ***J Gen Virol***. 2013 Dec;94 Pt 12:2724-8.

研究分担者（武冨　紹信、福原　崇介、安井　文彦）

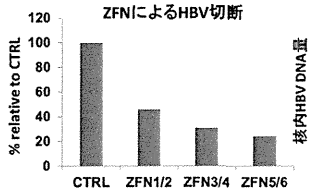
該当なし

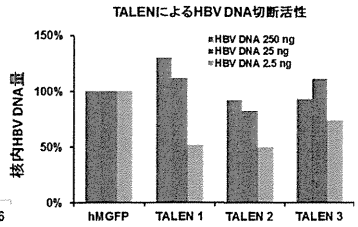
Ⅶ. Ⅲ (2 年間の研究成果) の概要図等

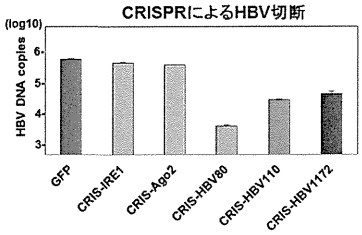
※ポンチ絵等でわかりやすく簡潔に説明してください。

基礎創薬開発

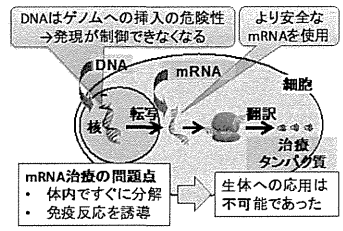
人工キメラ遺伝子の合成・最適化 (溝上、福原、安井)

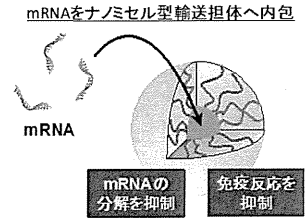




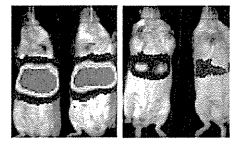


ナノ粒子でのDDS開発 (片岡)



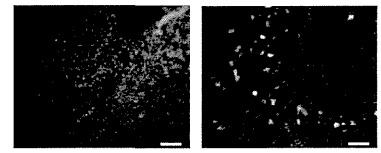


肝臓へのルシフェラーゼ発現mRNAの投与



→ ナノミセル型輸送担体による、肝組織での効率的なタンパク質発現

肝臓組織でのGFPタンパク質発現の分布

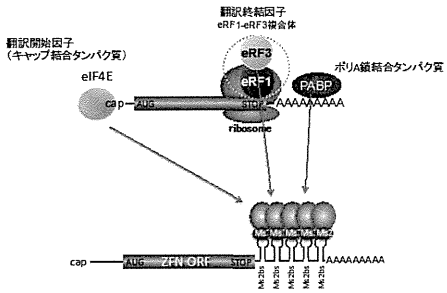


→ mRNAでは、ほぼすべての肝細胞でタンパク質発現
→ 治療応用に重要な性質

発現最適化

RNA安定化 (星野)

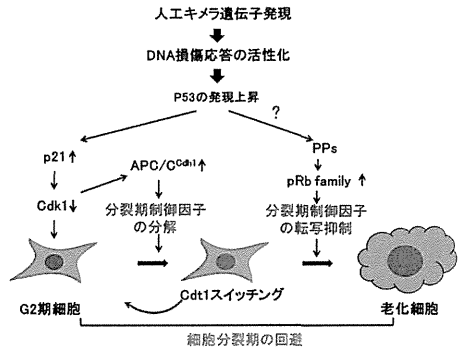
mRNAの翻訳と安定性に関わる因子の繋留による発現の効率化



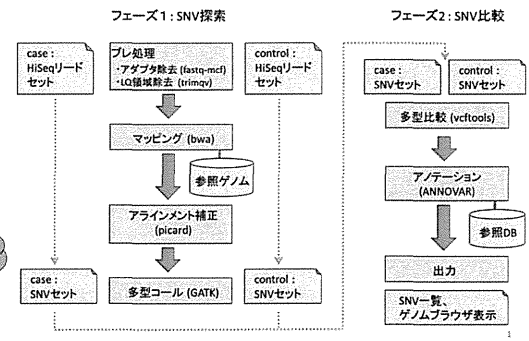
副作用の評価

DNA切断による細胞応答の検証 (中西)
全ゲノム解析での検証 (杉山)

人工キメラ遺伝子発現による細胞への副作用 (細胞老化誘導機構)

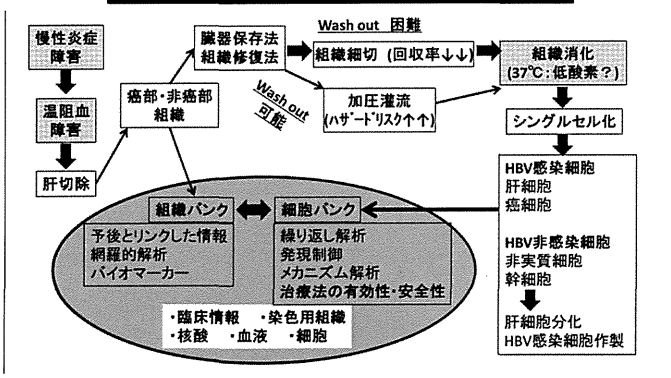


SNV比較パイプライン

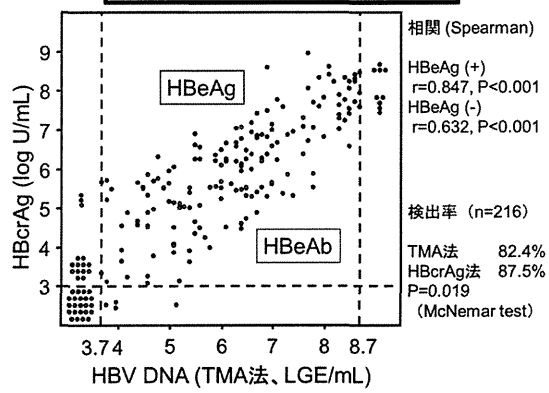


臨床応用準備

切除肝からのEx vivo系の開発 (武冨)



臨床的評価法の検討 (田中)



●研究代表者の研究歴等

※研究代表者に関するもののみを記載してください。(研究代表者には下線をつけて下さい)

・過去に所属した研究機関の履歴

昭和51年4月　名古屋市立大学医学部　第二内科
平成元年11月　King's College Hospital, Liver Unit
平成10年7月　名古屋市立大学　輸血部
平成12年11月　名古屋市立大学　臨床検査医学
平成13年11月　名古屋市立大学大学院医学研究科　臨床分子情報医学分野
平成20年10月　国立国際医療センター国府台病院　肝炎・免疫研究センター
平成22年4月　独立行政法人国立国際医療研究センター　肝炎・免疫研究センター

・主な共同研究者(又は指導を受けた研究者)

五條堀孝（国立遺伝学研究所）、脇田隆字（国立感染症研究所）、徳永勝士（東京大学）
田中靖人（名古屋市立大学）、Williams R. (King's College Hospital, Liver Unit)、Alter HA.(NIH)

・主な研究課題

ウイルス肝炎の病態と治療に関わるウイルス・宿主因子の解析とその応用による新規治療法・検査法の開発

・これまでの研究実績

※研究代表者の本研究の成果以外の実績も記載してください。
(成果概要Ⅵと重複するものや本研究成果によるものは、***太字・斜体***文字で記載してください)
※発表論文名・学協会誌名・発表年(西暦)、知的財産権の取得及び申請状況、研究課題の実施を通じた政策提言(寄与した指針又はガイドライン等)のうち、主なものを選択し、直近年度から順に記載してください。

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