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特許申請・取得

1. 特願2011-287603「IL-28Bの分析方法」溝上雅史、杉山真也、木村達治
2. PCT/JP2011/79353「B型肝炎ウイルス群を検出し、遺伝子多様性を評価するためのオリゴヌクレオチドのセット、並びにそれを用いた方法」溝上雅史、杉山真也、新井　理、田村卓郎
3. 特願2011-211647「C型肝炎患者の経過予測方法」溝上雅史、杉山真也
4. 特願2010-063622「C型肝炎の治療効果を予測するためのマーカー群、検査方法及び検査用キット」溝上雅史、田中靖人、徳永勝士
5. 特願2009-192615「C型肝炎の治療効果を予測するためのマーカー及びC型肝炎の治療効果の予測を行う方法並びにC型肝炎の予防又は治療剤」溝上雅史、田中靖人、徳永勝士
6. 特願2009-287243(特願2009-165795)「糖タンパク質の測定方法、肝疾患の検査方法、糖タンパク質定量用試薬および肝疾患病態指標糖鎖マーカー糖タンパク質」溝上雅史、伊藤清顕、成松久ほか、田中靖人、松原俊介ほか
7. 特願2009-165795「肝疾病病態診断指標糖鎖マーカー」溝上雅史、成松久ほか、田中靖人

平成24年度厚生労働科学研究費補助金(B型肝炎創薬実用化等研究事業)研究発表会
平成25年1月31日

「人エ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」(溝上班)
平成24年度進捗状況と次年度計画

主任研究者:溝上 雅史 (独)国立国際医療研究センター 肝炎・免疫研究センター
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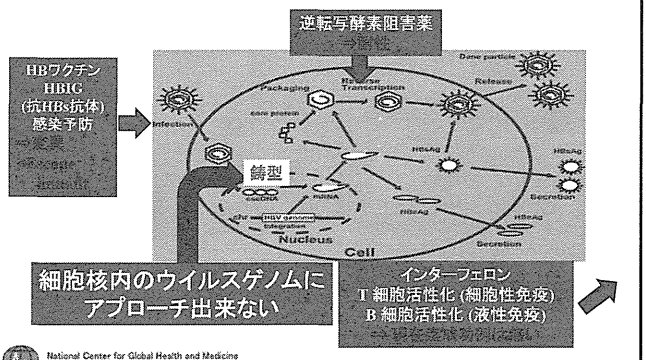
National Center for Global Health and Medicine
Research Center for Hepatitis and Immunology

HBVの完治を目指して!



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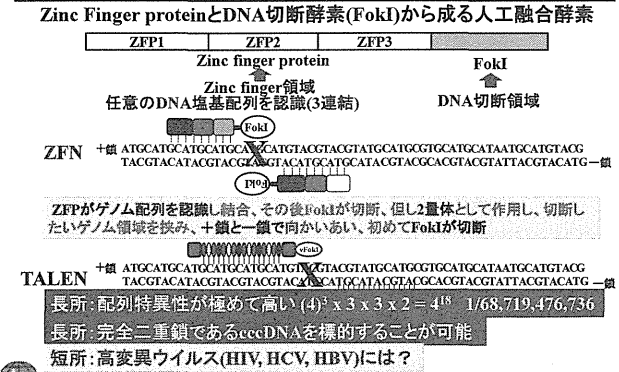
(溝上)

Zinc Finger Nucleases とTALENSとは?

Zinc Finger proteinとDNA切断酵素(FokI)から成る人工融合酵素



ZFPがゲノム配列を認識し結合、その後FokIが切断、但し2量体として作用し、切断したいゲノム領域を挟み、+鎖と一鎖で向かいあい、初めてFokIが切断

長所:配列特異性が極めて高い $(4)^3 \times 3 \times 3 \times 2 = 4^{18}$ 1/68,719,476,736

長所:完全二重鎖であるcccDNAを標的することが可能

短所:高変異ウイルス(HIV, HCV, HBV)には?

National Center for Global Health and Medicine
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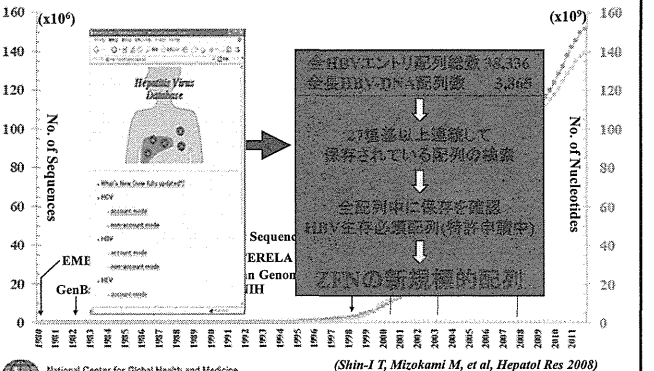
(溝上)

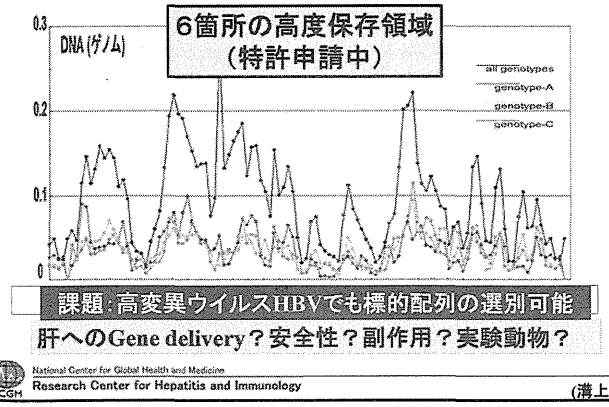
Hepatitis Virus Databaseを利用した新規標的配列の同定



(Shin-I T, Mizokami M, et al, Hepatol Res 2008)

National Center for Global Health and Medicine
Research Center for Hepatitis and Immunology
(溝上)

HBVゲノム上の変異分布



課題:高変異ウイルスHBVでも標的配列の選別可能

肝へのGene delivery?安全性?副作用?実験動物?

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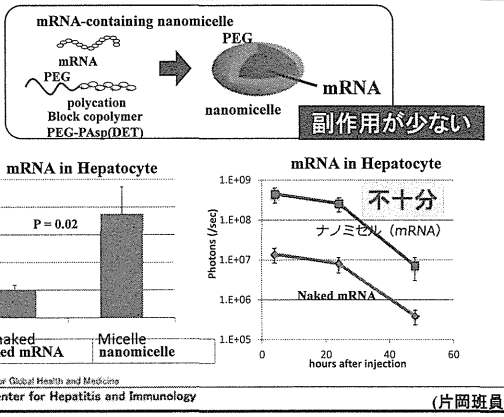
Research Center for Hepatitis and Immunology
(溝上)

Preservation of Injected mRNA in Liver



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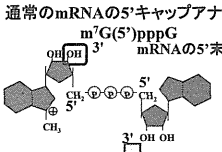
(片岡班員)

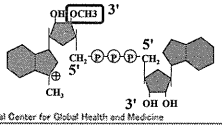
投与mRNAの発現効率を高めるには？

5′末端

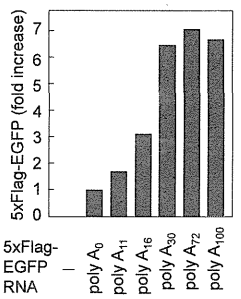
通常のmRNAの5′キャップアナログ
$m^7G(5')pppG$



アンチリバース キャップアナログ:
3′-O-Me-$m^7G(5')pppG$



3′末端



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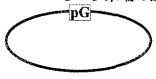
(星野班員)

投与mRNAの発現調節 –mRNAの環状化-

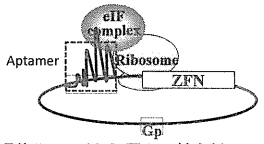
作製方法 (*in vitro*合成RNA)

pppG——OH
↓ ピロフォスファターゼで脱リン酸化
pG——OH
↓ 相補的オリゴによる5′—3′末端の近接化

↓ T4 RNAリガーゼ2による5′—3′末端の連結



環状型mRNA



環状化により翻訳因子の結合低下
1. EMCV IRES
（利点） 翻訳開始効率⇑
（欠点） 配列が長い(600~700塩基)
2. RNA Aptamer
(翻訳開始因子eIF4E, 4Gの結合部位)
配列が短い(80~100塩基)
→環状化効率⇑

発現効率の向上

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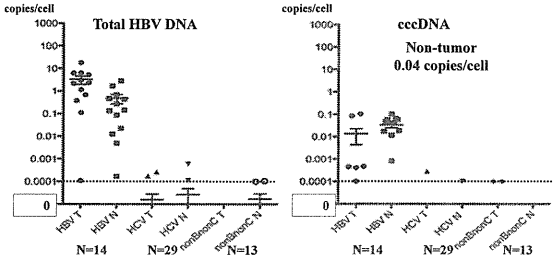
Research Center for Hepatitis and Immunology
(星野班員)

cccDNA quantification in liver tissue

HBVゲノム切断後の非相同性修復



肝細胞中のcccDNA量は思ったより少ない
⇒ HBVゲノム切断後の非相同性修復少ない？

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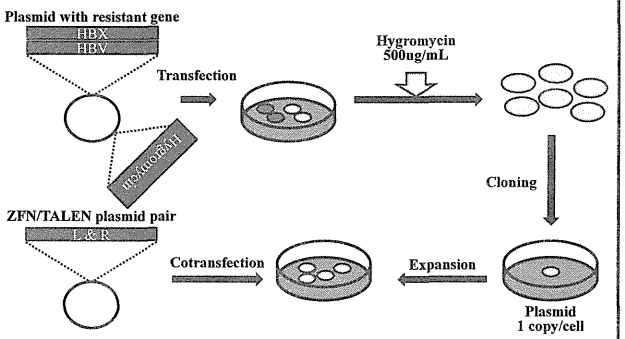
Research Center for Hepatitis and Immunology
(杉山班員)

HBVゲノム保有(cccDNA)細胞の樹立



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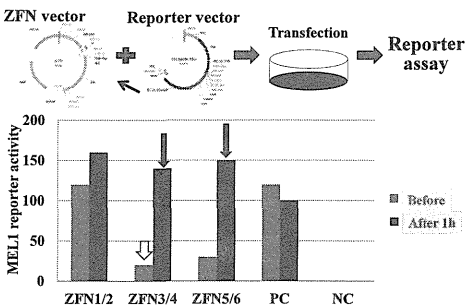
(杉山班員)

ZFNの標的としてのHBx Targeted Reporter Assay



配列により異なるが、確実にcccDNAを切断

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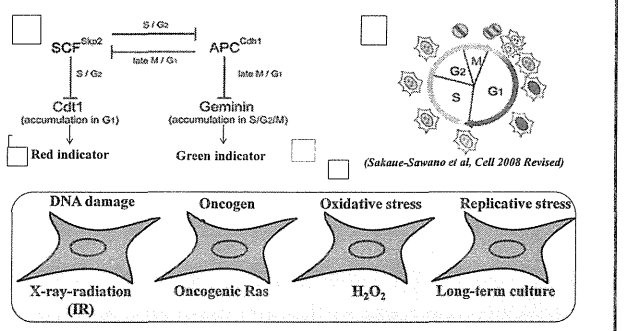
Research Center for Hepatitis and Immunology
(杉山班員)

ZFNの細胞に与える影響を細胞周期可視化で検討可能 (Senescence process)



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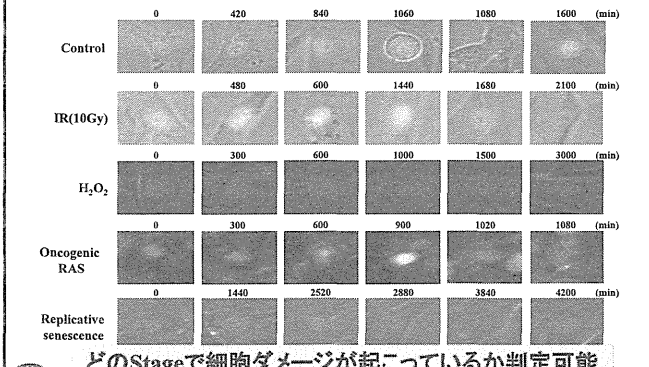
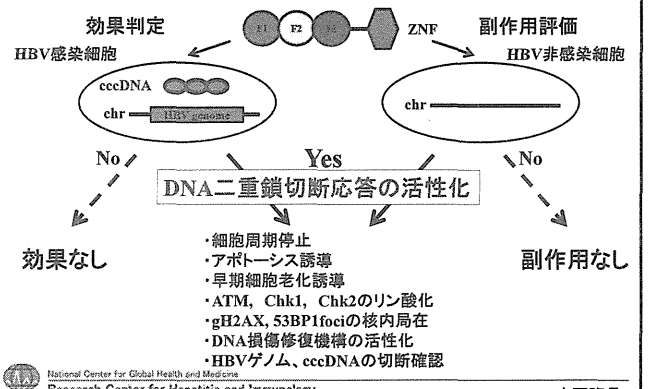
(中西班員)

Senescent Cells Undergo Mitosis Skip before Exit from Cell Cycle

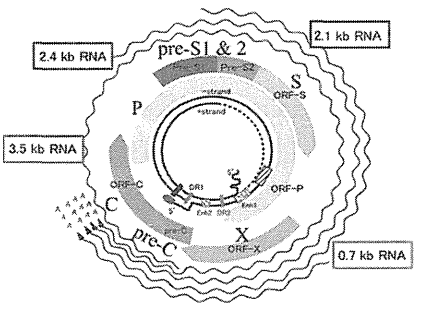


どのStageで細胞ダメージが起こっているか判定可能

ZNFによる効果および副作用評価



HBVのmRNAとウイルス抗原の測定系



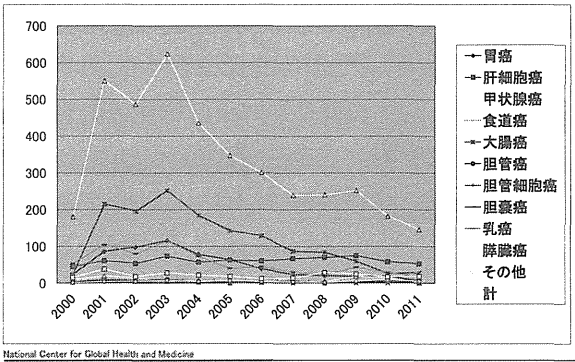
2.4 & 2.1 kb RNA
L -HBsAg
M-HBsAg
S-HBsAg
HBsAg

3.5 kb RNA
pregenome RNA
RT/Polymerase
HBeAg
HBcAg
p22c Ag
HBcrAg

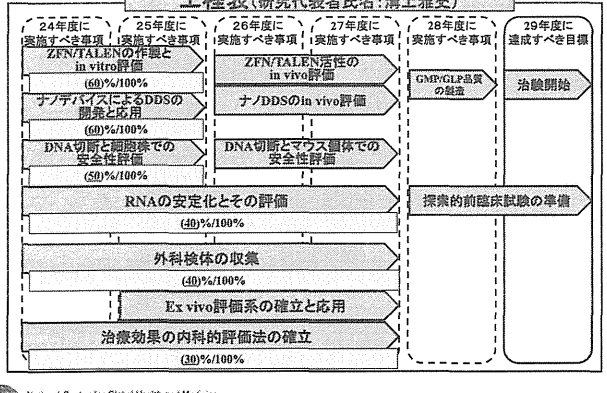
0.7 kb RNA
X Ag

(田中班員)

Tissue Bank臓器別登録数(2000 – 2011.10)



工程表(研究代表者氏名:溝上雅史)



利益相反について

利益相反の有無等(平成24年度)

- ア 利益相反の有無　　無
- イ 利益相反がある場合には具体的内容(以下に記載)

該当せず

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)**

① がん化学療法及び免疫抑制療法中のB型肝炎ウイルス再活性化予防対策の確立を目指したウイルス要因と宿主要因の包括的研究
(H24-肝炎-一般-004) (代表者:溝上 雅史)

② B型肝炎ウイルス再活性化予防対策の確立を目指した臨床的研究であり, HBVの完全排除を目的に創薬を目指す今回の研究事業とは異なるものである.

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24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)

該当せず

平成24年度 B型肝炎創薬実用化等研究事業『成果概要』

研究課題：B 型肝炎ウイルスの完全排除等、完治を目指した新規治療法の開発を目指した包括的研究

課題番号　：H24-B 創-肝炎--一般-012

予定期間　：H24 年度から H28 年度まで

研究代表者　：森屋恭爾

所属研究機関：東京大学

所属部局　：医学部附属病院

職名　：教授

年次別研究費(交付決定額)：1年目　88,918,000　円

Ⅰ. 研究の意義

(1)　HBV 感染症に対する根治療法確立、特に HBV 肝発癌抑制ならびに HBV cccDNA 排除可能な創薬は重要課題である。

(2)HBV キャリアからの肝不全、肝がん発生の防止策の確立が期待されている。

(3)HBV 関連症例における肝切除・肝移植後補助化学療法の確立が望まれている。:

Ⅱ. 研究の目的、期待される成果

(1)抗 HBV 薬スクリーニング、マウスモデルでの評価を通じて新規治療薬の候補化合物を取得する。

(2)HBV DNA の複製制御、遺伝子発現調節の分子機構、non-coding RNA による HBV 複製制御、HBV 複製における肝細胞分化レベルの関与等を明らかにし新規創薬標的、戦略を見出す。

(3)HBV により変動する non-coding RNA の同定機能解析等を行い、病態発現機構解明へ繋げる。

(4)高機能肝組織培養系を駆使し新たな HBV 増殖モデルを作出する。

(5)HBV 複製細胞選択的な遺伝子治療用アデノウイルスベクターを開発する。

(6) HBV 関連症例、特に HBs 抗原陰性 HBc 抗体陽性患者への肝切除・肝移植術後補助化学療法を確立する。

Ⅲ. 1年間の研究成果

・研究代表者　森屋恭爾

1)HBx 遺伝子発現トランスジェニックマウスにおいて Mevalonate pathway が亢進していることを見出した。

(2)肝細胞へのアポトーシス誘導導能から statin は肝発癌抑制および治療薬となる可能性がある。HBx トランスジェニックマウスへの statin 投与実験を開始し、STAT3, HIF1-α 遺伝子発現抑制などの基礎知見を取得した。

・研究分担者

(1)HBV コアプロモーター活性阻害剤スクリーニングを行い海洋抽出創薬ライブラリーから抑制画分を見出した。質量分析によって HBV 感染によるトリアシルグリセリド変動を明らかにした(森石)。

(2)HBV RNA と相互作用する可能性があり癌抑制機能を持つ microRNA let-7 の機能が、HBV-RNA 存在下において減弱することを見出した（小池)。

(3)核内の各 HBV DNA フォームを含む密度分画の分離技術を確立した。エンハンサーII 内に HBV 遺伝子型 C に特徴的な遺伝子発現制御エレメントが存在することが示唆された（鈴木)。

(4)HBx発現によって発現が抑制される4種の機能未知のlong-noncoding(X-lnc)RNAを同定した(北川)。
(5)SILAC法により、HBV複製に伴って発現変動する核タンパク質、膜タンパク質を解析した。HBV感染の新規検出系としてレポーター遺伝子挿入HBVゲノムを作製し、発現を確認した(福原)。
(6)ヒトiPS細胞から肝細胞系細胞への分化誘導と肝幹細胞様細胞の分離、成熟化肝細胞への誘導培養系を構築した。種々のHBx変異体発現系を作製した(朝比奈)。
(7)in vitro肝組織モデル作製へ向けて、HBV複製肝がん細胞と内皮細胞、更に星細胞株を共培養しネットワーク構造が形成されることを見出した(田川)
(8)HBV複製細胞での治療用遺伝子の選択的な切り出し、環状増幅を可能にする新規アデノウイルスベクター(AdV)を開発すべく、基盤となる各HBV遺伝子発現AdVを作製した(斎藤)。
(9) 初発で前治療歴のない肝細胞癌切除症例682例の予後を当科1997年から2011年までの症例で検討し、特に肝炎ウイルス別の生存率を解析した。非B非C型肝炎症例では、HBc抗体陽性例の予後がHBc抗体陰性例の予後よりも有意に良好であることが示された(國土)。

Ⅳ. 平成25～28年度の課題

1) HBV感染ヒト肝細胞キメラマウスでの抗ウイルス効果／肝機能改善効果の評価、患者組織におけるHBV感染による代謝変化の知見を蓄積し、statinのB型肝炎治療薬としての有用性を明らかにする。
(2)日本におけるHBs抗原陽性statin内服患者の発癌率についてコホート研究を行う。
(3)HBV転写、DNA複製等に対する阻害剤を探索し、新規抗HBV薬の開発へ繋げる。
(4)核内HBV DNAの構造変換、エピジェネティック修飾、HBxの機能を解明しHBV複製、遺伝子発現機構の全容を明らかにする。
(5)microRNAによるHBV生活環制御、HBVによるmicroRNA機能撹乱惹起の機構を明らかにする。
(6)lncRNAとHBVとの関連は未だ不明である。同定したX-lncRNAの機能解析からlncRNAによるHBV生活環制御、肝病態誘発の可能性を探る。
(7)HBV感染複製に伴って発現変動する核因子、膜因子のHBV生活環、肝病態発現における役割を解明する。
(8)ヒトiPS細胞由来の細胞分化度を調節し得る培養系を確立し、細胞分化度の変化がHBV生活環に与える影響を解析する。
(9)ヒトES/iPS細胞由来肝細胞による肝組織モデルでのHBV増殖系を確立。肝微小環境を持つ肝組織チップでのHBV増殖系の構築、HBVレセプター発現による感染肝組織モデルの構築を目指す。
(10)HBVプロモーターからCreを発現するAdV、人工ヌクレアーゼなど治療用遺伝子を発現するAdVなどを作製し、既存法とは一線を画した特異的遺伝子治療用Advを確立する。
(11) 術後補助療法の検討にあたり、さらにretrospectiveにウイルスマーカー別の病理組織学的因子を検索する。非B非C型肝炎の発症にはNASHやNAFLDの存在が示唆されており、切除標本検体においてその存在を証明する。

Ⅴ. 行政施策への貢献の可能性

(1)日常既に広く使用されているstatinによる発癌抑制が明らかになれば、B型肝炎からの肝発癌抑制としてstatin治療が迅速に普及し医療費の軽減に直結する。
(2)HBV 複製、遺伝子発現の選択的阻害剤を単離・同定することで、不完全な現行治療法を補完する新規クラスの抗HBV療法の開発が期待できる。
(3)in vitro肝組織モデルによるHBV感染増殖系は阻害剤スクリーニングに極めて有用性が高い。
(4)AdVは肝臓への遺伝子導入効率が非常に高い。本研究でHBV複製細胞特異的な導入技術を確立することにより高安全性の治療用AdVが作製され、難知性肝疾患の治療選択肢がふえる。
(5)術後補助療法の確立により、HBV再燃防止が可能となり術後生存率向上に寄与する。従来の非B型患者の中にHBVキャリアが存在することを示し、注意喚起する波及効果も期待される。