# 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：革新的な動物モデルや培養技術の開発を通じたHBV排除への創薬研究
課題番号　：H24-B創-肝炎-一般-016
予定期間　：H24年度からH28年度まで
研究代表者　：茶山一彰
所属研究機関：広島大学
所属部局　：大学院医歯薬保健学研究院
職名　：教授
年次別研究費(交付決定額)：1年目　100,000,000　円2年目　170,000,000　円

## Ⅰ．研究の意義

(1)B型肝炎の治療は核酸アナログとIFNにより改善したが完全に排除することは出来ていない。
(2)ウイルスを完全に、かつ安全に排除することは患者の治療のみならず、患者の精神的負担、経済的負担を軽減することができ、医療経済の負担軽減にも貢献する。

## Ⅱ．研究の目的、期待される成果

(1)B型肝炎ウイルスを安全に、かつ完全に排除(HBs抗体陽性化)する新規治療を開発する。
(2)この目的の達成に資する動物モデル、細胞培養系を改善し、治療の有効性、安全性を評価する。
(3)日本発の新しい治療の開発は患者の治療からの解放のみならず、日本の経済の活性化に寄与し、また貿易収支の医療面での赤字の改善にも貢献する。

## Ⅲ．2年間の研究成果

・研究代表者（茶山一彰）
(1)B型劇症肝炎モデルに対する抗体治療の作製用の抗FAS-L発現細胞を作製した。
(2)ヒト化TK-NOG mouseを用いてB型肝炎ウイルスの感染、治療効果の確認が出来ることを明らかにした(Kosaka et al. BBRC 2013)。この系とヒトPBMCによる肝炎モデルを作製した。また長期間ヒト化が保たれるcDNA-uPA/SCIDマウスHBV感染系を構築した(立野班員との共同研究)。
(3)uPA/scid肝細胞移植マウスを用いて感染により肝細胞で自然免疫が作動すること、次世代シーケンサーによるmRNAの発現解析によりこれまでに報告されていないサイトカインの発現誘導が起こること、特定のmiRNAが誘導されること(田原班員との共同研究)、HBV感染によりIFNによるISGの誘導の一部が阻害されることを明らかにした。また、ヒト肝細胞キメラマウス由来の初代培養肝細胞でHBV増殖を支持する宿主因子の同定が可能であることを明らかにした。
(4)CRISPR/Cas9を用いて高効率にHBVの増殖を抑制する系を構築した(山本班員との共同研究)。
(5)キメラマウスにHBs抗体を大量に投与、ウイルスの減少を確認、ヒトでの効果を検証した。
・研究分担者(瀬谷司) (1) HBV感染の自然免疫応答をマウスhydrodynamicsモデルで解析した。a) マウス in vivo でHBV 複製制御にIRF3/7 は関与するが、MAVS、TICAM-1 は関与しない。よってHBV はDNA phase でIRF3/7 依存性のtype I IFN誘導系に検知される。b) HBV plasmid はRagによる獲得免疫を起動するが、MyD88-/- マウスでRag-/- と同等の持続感染が誘導できた。
・研究分担者(加藤博己) ＮＴＣＰ安定発現株をHeLa, HepG2の２種類を用いて樹立し、ＨＢＶ複製を認めることができた。アルブミンプロモーター存在下で肝臓特異的にＮＴＣＰを発現するトランスジェニックマウスを作製中であり、現在germ line transmissionを確認中である。
・研究分担者（立野知世）14週間のHBV長期感染cDNA-uPA/SCIDホモキメラマウス肝臓の病理組織観察では線維化、Apoptosisはなく、肝細胞の増大が見られ、炎症や線維化に関与するマウス遺伝子発現に差はなく、増殖抑制に関与する遺伝子発現の低下傾向がみられた。より長期間のHBV感染の影響を調べるため、cDNA-uPA/SCIDヘテロキメラマウスへのHBV感染実験を実施している。
・研究分担者(山本卓) HBVの転写活性化領域に特異的に結合するTALEおよびHBVのコアタンパク質遺

伝子を切断して破壊する TALEN を作製し、HepG2 細胞を用いて HBV 増殖抑制効果を観察した。また、CRISPR/Cas9 を用いた HBV 遺伝子破壊を検討するため独自の発現ベクターを構築した。

・研究分担者(田原栄俊) B型肝炎患者の血液中に存在するマイクロ RNA 関する報告は、これまでにあるが、次世代シークエンスを用いたマイクロ RNA 発現解析と配列解析を行い、B型肝炎患者でマイクロ RNA の発現量の変化と共に、IsoMiR の変化が顕著に起こっていることを見いだした。

・研究分担者(丸澤宏之) 任意の時期に肝細胞に HBV 抗原タンパク質を発現し、肝炎としての免疫応答を惹起する新規モデルマウスの樹立を進めている。薬物投与により HBV 蛋白、Mx 蛋白を発現するマウスを作製、交配しマウス肝組織における HBs 抗原の発現などの解析を行っている。

・研究分担者(Hussein H Aly) In a trial to identify factors that block HBV life cycle, we screened 500 kinases (key regulators of proteins function and signaling pathway) for its function on HBV suppression using shRNA library. We identified 5 kinases suppressing HBV significantly; we are analyzing recently the mechanism of suppression.

・研究分担者(坂口剛正) HBV 広島株の各蛋白質の発現系を確立し、P 蛋白質が全般的に転写を抑制することを見いだした。さらにいくつかのウイルス蛋白質が単独発現で細胞から放出されることを見いだして、それぞれの蛋白質のウイルス粒子形成における役割を解明している。

・研究分担者(阿部弘美) (1)1.4 倍長の HBV DNA construct と CRISPR/Cas9 による HBV 増殖抑制系を用いて、作製した CRISPR/Cas9 の系が肝細胞内の HBV を 1/5 程度に減少させることを確認した。

## Ⅳ. 平成 26～28 年度の課題

(1)uPS/scid 劇症肝炎、TK-NOG 持続肝炎モデルを使用、抗体、細胞性免疫による肝炎の制御を可能にする方法を開発。(2)ヒト肝細胞キメラマウス由来の初代培養肝細胞を用いて HBV 感染増殖に重要な宿主因子を同定。(3)CRISPR/cas9 の系をアデノウイルスベクターで供給する系を構築。

## Ⅴ. 行政施策への貢献の可能性

(1)HBV を完全に排除する治療を開発し患者を治療から解放、国の医療費負荷を軽減できる。日本発の新治療の開発は経済の活性化に寄与し、医療面の貿易収支の赤字の改善にも貢献する。

## Ⅵ. 本研究の成果(発表論文・ガイドライン・マニュアル等)

【研究代表者】茶山一彰


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【研究代表者】茶山一彰、【研究分担者】阿部弘美


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【研究分担者】立野知世

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① アクチベータトランスジェニックマウス」、PCT/JP2013/062806 (H25年4月25日出願)

【研究分担者】瀬谷司

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【研究分担者】加藤博己

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【研究分担者】山本卓

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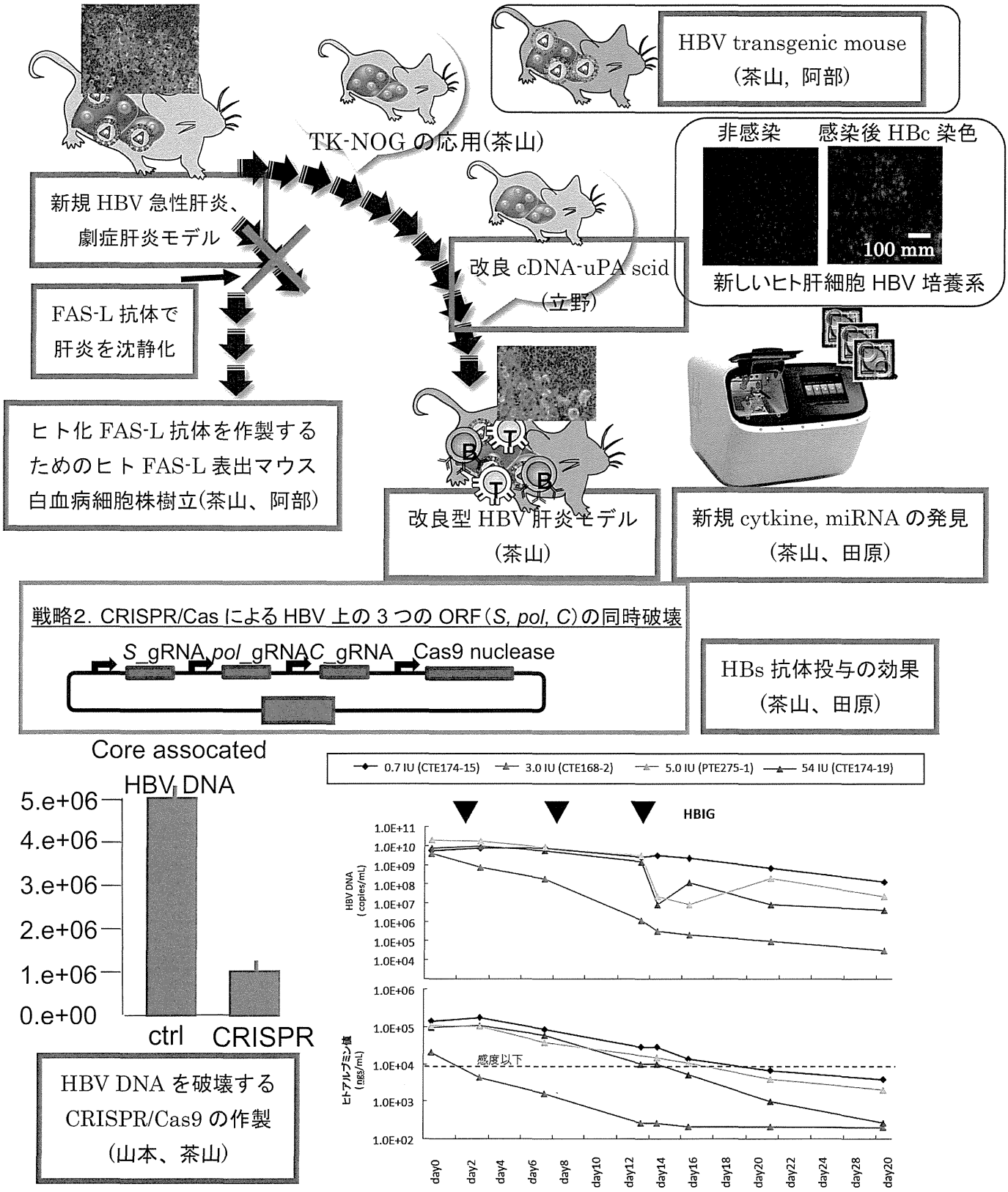
**知的財産権の取得及び申請状況**

1. B型肝炎患者の血清中マイクロRNA 診断マーカー　発明者：田原栄俊、茶山一彰（広島大学・大学院医歯薬学保健学研究院）申請者：広島大学　特許申請準備中
2. C型肝炎ウイルスの感染抑制剤　発明者：土方誠，阿部雄一，脇田隆字，茶山一彰(広島大学・大学院医歯薬学保健学研究院)出願者：国立大学法人京都大学、国立感染症研究所長が代表する日本国、国立大学法人広島大学、東レ株式会社　出願日：2013年3月19日　出願番号：特願 2012－536601
3. インターフェロン療法の効果予測用マーカー　発明者：茶山一彰、(広島大学・大学院医歯薬学保健学研究院) 越智秀典、中野力太　出願者：国立大学法人広島大学、大日本住友製薬株式会社、独立行政法人理化学研究所　出願日：2012年2月15日　出願番号：特願2012－031178
4. 肝細胞癌への進展予測マーカー　発明者：茶山一彰、(広島大学・大学院医歯薬学保健学研究院) 越智秀典、三木大樹　出願者：国立大学法人広島大学、大日本住友製薬株式会社、独立行政法人理化学研究所　出願日:2012年2月10日　出願番号:特願2012－027735　公開番号:特開2012－179047
5. B型肝炎発症ヒト肝細胞キメラモデル動物の作製方法　発明者：茶山一彰(広島大学・大学院医歯薬学保健学研究院)　出願者：国立大学法人広島大学　出願日：2011年8月31日　出願番号：特願2011-189317　公開番号：特開2013-048606

## Ⅶ. Ⅲ（2 年間の研究成果）の概要図等



●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61年～平成2年国家公務員共済組合連合会虎の門病院内科
消化器内科学（肝臓病学）に関する臨床研究を行った。

・平成2年～平成12年国家公務員共済組合連合会虎の門病院内科　医長
消化器内科学（肝臓病学）に関する臨床研究を行いつつ、肝炎ウイルスに関する分子生物学的研究を行った。

・平成12年9月～文部科学教官教授（広島大学内科学第一講座）
消化器内科、循環器内科に関する診療、臨床研究を行いつつ、肝炎ウイルスに関する分子生物学的研究、ヒトの遺伝素因と疾患に関する研究、動物を用いた肝炎ウイルス肝炎モデルに関する研究を開始した。

・平成14年4月～広島大学大学院・医歯薬学総合研究科・創生医科学専攻・先進医療開発科学講座・分子病態制御内科学（旧内科学第一講座）教授
消化器内科、循環器内科に関する診療、臨床研究を行いつつ、肝炎ウイルスに関する分子生物学的研究、ヒトの遺伝素因と疾患に関する研究、動物を用いた肝炎ウイルス肝炎モデルに関する研究をさらに展開している。

・主な共同研究者(又は指導を受けた研究者)

・指導を受けた研究者：熊田博光

・共同研究者：中村祐輔[シカゴ大学],松浦善治[大阪大学微生物学研究所],脇田隆字[国立感染症研究所],溝上雅史[国立肝炎免疫センター],金子周一[金沢大学],高倉喜信[京都大学],Jia-Horng Kao [National Taiwan University], Jake Liang [NIH], Susan Uprichard[Loyola University], Harel Dahari[Loyola University].

・主な研究課題

1. B型肝炎ウイルスの増殖に関する研究
2. B型慢性肝炎の治療に関する研究
3. C型肝炎ウイルスの増殖とインターフェロン治療効果との関連の研究
4. C型肝炎ウイルスのgenotypeに関する研究
5. 肝細胞癌の治療と再発防止に関する研究
6. 消化器癌の形態学的、分子病理学的研究
7. 内科学（消化器内科学）に関する研究

・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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