財では、生体に存在する細胞そのものでは知財が成立しない。請求項では、「肝細胞様細胞」として知財化が目指されている。当然、現状の特許判断ではこれら細胞は知財化困難であることは知財にかかわるものであれば衆知のことではある。これまでの多くの再生医療関連出願では、当初から知財化を断念して請求項としてあげないか、あるいはおざなりの請求項として記載されるのみである。本請求項17では、「請求項1～16の方法得られた肝細胞様細胞」とされている。これは、product-by-process特許といわれるもので、バイオ知財ではまだ特許化に成功した例は少ないが、あえての記載は知財戦略的に合理的であると考える。なんとなれば、現在行われているTPP交渉の過程で、知財のグローバル化という柱があり、product-by-process特許を認めることとなれば、知財勢力図を塗り替えかねないからである。現状では、「モノ」としての知財化を横目で見たチャレンジングな請求項であるといえよう。ただし、実施例でチャレンジングの程度、前向きさを納得させるデータがないのは残念である。ついで、請求項18では、「請求項17に記載の肝細胞様細胞を含む細胞製剤」として、再生医療等製品としての知財化を射程に入れている。

肝細胞の再生は、再生医療そのものとしての知財よりも、創薬スクリーニングへの展開のほうが、市場的にも大きく魅力的である。そこで、請求項19及び20は、創薬スクリーニングを射程にいれた記載となっている。本特許出願がスクリーニングへの展開を念頭にいれていることは、請求項19でCYPなど代謝活性スクリーニングへの展開を可能にしていること、請求項20で薬剤の肝毒性スクリーニングにかかる言及があることで理解できる。肝細胞を用いるスクリーニング系を念頭に入れた特許出願で、薬剤（創薬）スクリーニングで代謝活性と毒性評価に2本柱を理解しているものがほぼなく、その観点から本特許出願は、再生医療関連特許出願として出色であるといえる。

確かによく検討され、「練られた」請求項であるが、欲を言えばもっと広範囲をおさえる知財として出願することは可能であった。請求項1では、人工多能性幹細胞からの肝細胞への分化誘導へと限定されている。これは、ES細胞を含む多能性幹細胞、あるいは体性幹細胞でも「多能性」を標榜しているものがあることから、それらを広範に出発原材料として請求項を作りこむべきであった、といえる。人工多能性幹細胞に限定しているのが、実はES細胞を用いての先行特許（出願）があり、当該知財への抵触を想定していたのであれば、そもそも知財として成立し得ない。加えて、知財を活用して細胞製剤などを製造販売する起業にとって、出発原材料細胞がiPSである

ことにメリットはないため、自ら多能性を確認して、「知財に抵触しているので、ロイヤリティーを支払います」という企業があるとは思えず、独占を大命題とする知財戦略の大きな穴ができてしまう。これらの点は、先行知財調査を実施していないため、これ以上の言及はしないこととする。人工多能性幹細胞の中でも、GATA-4 陽性が本知財での分化誘導法で重要なマーカーであるなら、「GATA-4 陽性であって、いくつかの胚葉に分化しうる能力(可能性)を有する細胞。いくつかの胚葉とは、内胚葉、中胚葉、外肺葉のすべて、いずれかを指す。」として、あえて多能性幹細胞という term による知財調査から隠れるように請求項を記載するとの戦略はあり、企業等であればその戦略をとっているかもしれない。また、「肝細胞」へと誘導する方法となっているが、肝細胞の定義が不明であること、生体内の肝細胞との差異を明確にしていないため、物質特許としての展開を自ら否定してしまっている。肝細胞ではなく、たとえば肝細胞様細胞あるいは内胚葉様細胞として、人工的に *in vitro* で製造可能な細胞への展開性を確保しておくべきであった。指摘したいことは、「肝細胞」の定義が不明確であることにより、クレーム逃れの余地が大きくなっているという点にある。また、肝細胞と肝細胞様細胞という用語が、明確な差を提示されるに記載されているのも、知財を弱くしている。細胞製剤を主眼とした知財であるなら、肝細胞の定義としてアルブミン陽性細胞、アンモニア代謝活性を有する細胞（あるいはオルニチン・カルバモイル転写酵素を発現している細胞）のように、治療標的を明確化した定義が有効である（範囲は縮減する可能性はあるいので注意)。請求項 17 では、「治療法」という記載がないので、米国と欧州いずれにも展開しようとすると、治療法としての請求項がないことは、残念であった。

請求項 18 では、「肝細胞様細胞を含む細胞製剤」とある。本特許出願の実施例では、疾患モデル動物でのデータがない。治療目的特許としては、実施例がないことは根本的な課題で、当該請求項は成立しないであろう。

請求項 19 および 20 では、確かにスクリーニングへの展開可能性を期待させるが、使用している iPS 細胞のラインが 1 ラインのみであり、複数ラインを用いるのがスクリーニングの王道であることを考えると、3 ラインくらいの iPS 細胞は用い、ばらつきが少なく産業応用性があることは明示すべきであった。

ここで、「特許 drafting でもっと大切なことはなにか」という本分担研究の本旨へと展開したい。

答えは、「**imagination**」と述べたい。

D. 考察

Case study で用いた出願特許で、製品イメージをもとに、請求項を以下のように変えてみよう（スクリーニングに焦点）

【請求項 1】多能性幹細胞を分化誘導して得られた肝細胞を用いる薬物代謝スクリーニングシステム及び／又はキット、および肝毒性スクリーニングシステム及び／又はキット

【請求項 2】多能性幹細胞から肝細胞を得る方法が以下の工程（１）及び（２）を含む請求項１の薬物代謝スクリーニングシステム及び／又はキット、および肝毒性スクリーニングシステム及び／又はキット：

（１）人工多能性幹細胞を内胚葉様細胞へと分化させる工程；

（２）工程（１）で得られた内胚葉様細胞を肝細胞様細胞へと分化させる工程であって、ヒストン脱アセチル化酵素阻害剤の存在下及び／又は酸化ストレス負荷条件下で少なくとも一部の培養を実施する工程

【請求項 3】請求項 1～2 に記載の、多能性幹細胞を分化誘導して得られた肝細胞を用いる薬物代謝スクリーニングシステム及び／又はキットであって、以下の工程（ｉ）及び（ｉｉ）を含む、被検物質の代謝を評価する方法：

（ｉ）肝細胞様細胞に被検物質を接触させる工程；

（ｉｉ）被検物質の代謝を測定する工程。

【請求項 4】請求項 1～2 に記載の、多能性幹細胞を分化誘導して得られた肝細胞を用いる肝毒性スクリーニングシステム及び／又はキットであって、以下の工程（ｉ）及び（ｉｉ）を含む、被検物質の毒性を評価する方法：

（ｉ）肝細胞様細胞に被検物質を接触させる工程；

（ｉｉ）工程（ｉ）後の肝細胞様細胞の状態を調べる工程。

実施例で補強・クレームアップも念頭に

【請求項 1】多能性幹細胞を分化誘導して得られた肝細胞を用いる薬物代謝スクリーニングシステム及び／又はキット、および肝毒性スクリーニングシステム及び／又はキット

【請求項 2】多能性幹細胞から肝細胞を得る方法が以下の工程（１）及び（２）を含む請求項１の薬物代謝スクリーニングシステム及び／又はキット、および肝毒性スクリーニングシステム及び／又はキット：

（１）人工多能性幹細胞を内胚葉様細胞へと分化させる工程；

（２）工程（１）で得られた内胚葉様細胞を肝細胞様細胞へと分化させる工程であって、ヒストン脱アセチル化酵素阻害剤の存在下及び／又は酸化ストレス負荷条件下で少なくとも一部の培養を実施する工程

【請求項3】請求項1～2に記載の、多能性幹細胞を分化誘導して得られた肝細胞を用いる薬物代謝スクリーニングシステム及び／又はキットであって、以下の工程（ｉ）及び（ｉｉ）を含む、被検物質の代謝を評価する方法：

（ｉ）肝細胞様細胞に被検物質を接触させる工程；

（ｉｉ）被検物質の代謝を測定する工程。

【請求項4】請求項1～2に記載の、多能性幹細胞を分化誘導して得られた肝細胞を用いる肝毒性スクリーニングシステム及び／又はキットであって、以下の工程（ｉ）及び（ｉｉ）を含む、被検物質の毒性を評価する方法：

（ｉ）肝細胞様細胞に被検物質を接触させる工程；

（ｉｉ）工程（ｉ）後の肝細胞様細胞の状態を調べる工程。

製品のイメージの観点から請求項を記載してみた。ここから普遍化できることは回帰である。すなわち、再生医療等製品・創薬スクリーニングを製品イメージとして念頭におき、本特許が産業利用される場合の活用法をイメージすると、創薬スクリーニングではHTSで活用可能な請求項であることが肝心である。iPS細胞を用いる創薬スクリーニング特許の多くは、分化誘導法に焦点が当てられており（アカデミア発の知財の限界であるが）、いわばphenotype screeningでしか使用できない。創薬スクリーニングでは、HTSが求められるので、HTSを念頭に入れた知財請求項を構成させるべきである。また、創薬スクリーニングであれば、その知財に由来する製品（HTSキット）を活用するヒト（スタッフ）、すなわちニーズを考慮すべきである。このニーズとは、当該知財による製品が活用される場はどこなのか、という問いに対する答えそのものである。創薬スクリーニングであるなら、製薬企業であり、活用される場のpatternを想定するとハブタイプでありスポークタイプではない、ということである。

では、使える特許を構築するにはどのようにしたらよいのだろうか。使える特許とは、研究論文のように積み上げるのではなく、製品イメージから実施例と請求項を記載し、特許の枠組に実施例をはめ込んでいる知財である。企業では、必要な知財の枠組みを考えて、それに入れ込む実施例を積み上げていくのであろうが、再生医療の主役を担うアカデミアでは、そうは行かない。既存実施例を生かし、枠組みを構築するしかなく、そのような制限の元でよい請求項を書き上げていくのは、弁理士の腕の見せ所といえよう。当然、実施例を積み上げるアカデミアにも、請求項を記載する弁理士にも、imaginationは欠くべからざる素養であるといえる。

E. 結論

「Imagination」とは？

再生医療知財の領域においては、出願された特許・知財が、どのような製品・サービスに活用されるのか、その製品・サービスを社会に提供する企業の企業戦略はどのようなものか、ひいてはその知財が、社会をよりよいものにするために、どのように活用されるべきか、という「想い」をもつということである、と提言しよう。

F. 研究発表

1. 論文発表

1. Matsuyama A. Translational research in regenerative medicine: A translational gap. Pharmaceuticals Policy and Law. 2013:15.163-172.
2. Shudo Y, Miyagawa S, Okura H, Fukushima S, Saito A, Kawaguchi N, Matsuura N, Shimizu T, OkanoT, Matsuyama A, Sawa Y. Addition of mesenchymal stem cells enhances the therapeutic effects of skeletal myoblasyt cell-sheet transplantation in a rat ischemic cardiomyopathy model. Tissue Eng, part A. 2013 Oct 29.
3. Okura H, Soeda M. Miyagawa S, Sawa Y, Ichinose A, Matsuyama A. *in situ* reprogrammed spermine treated adipose –tissue-derived multi-lineage progenitor cells improve left ventricular dysfunction in a swine chronic myocardial infarction model. Proceedings of the 10th International Congress on Coronary Artery Disease. 2013. 39-42.
4. Okura H, Soeda M. Morita M, Ichinose A, Matsuyama A. Transplantation of human adipose tissue-derived multi-lineage progenitor cells but not adipose tissue-derived stromal/stem cells reduces serum cholesterol in hyperlipidemic Watanabe rabbits. Proceedings of the 10th International Congress on Coronary Artery Disease. 2013. 51-54.
5. Okura H, Soeda M. Morita M, Ichinose A, Matsuyama A. Transplantation of adipose tissue-derived multi-lineage progenitor cells reduces serum cholesterol in hyperlipidemic Watanabe rabbits. Proceedings of the 10th International Congress on Coronary Artery Disease. 2013. 51-46.
6. Moriyama H, Moriyama M, Sawaragi K, Okura H, Ichinose A, Matsuyama A, Hayakawa T. Tightly regulated and homogeneous transgene expression in human adipose-derived mesenchymal stem cells by lentivirus with tet-off system. PLoS One. 2013 Jun 12;8(6):e66274.
7. Kawase R, Ohama T, Matsuyama A, Matsuwaki T, Okada T, Yamashita T, Yuasa-Kawase M, Nakaoka H, Nakatani K, Inagaki M, Tsubakio-Yamamoto K, Masuda D, Nakagawa-Toyama Y, Nishida M, Ohmoto Y, Nishihara M, Komuro I, Yamashita S. Deletion of progranulin exacerbates atherosclerosis in ApoE knockout mice. Cardiovasc Res. 2013 Oct 1;100(1):125-33.
8. Yuasa-Kawase M, Masuda D, Yamashita T, Kawase R, Nakaoka H, Inagaki M, Nakatani K, Tsubakio-Yamamoto K, Ohama T, Matsuyama A, Nishida M, Ishigami M, Kawamoto T, Komuro I, Yamashita S. Patients with CD36 Deficiency Are Associated with Enhanced Atherosclerotic Cardiovascular

Diseases. J Atheroscler Thromb. 2013;20(5):514-5.
9. 大倉華雪・松山晃文 細胞医療での申請にあたっての注意点—品質の観点から— 先進医療 NAVIGATOR II 再生医療・がん領域の実用化への TOPICS 2014. pp5-8
10. 松山晃文 再生医療とレギュラトリーサイエンス -早期実現にむけて合理的な理解を-」ヒューマンサイエンス 2013: (7).28-31
11. 松山晃文 再生医療の規制と今後の動向 リーガルマインド 2013:337.36-102
12. 松山晃文 再生医療の早期実現化と国際展開に向けた研究開発支援 再生医療 2013:12(2).133-134.
13. 松山晃文：「再生医療とレギュラトリーサイエンス -早期実現にむけて合理的な理解を-」ヒューマンサイエンス 2013: (7).28-31.
14. 松山晃文：「再生医療の規制と今後の動向」リーガルマインド 2013:337.36-102.

2. 学会発表

1. 再生医療が拓く明日へ—研究者の想いと産業界への願い—・松山晃文・東西合同薬事法規（研究）委員会・6 月 21 日
2. 高度医療とトランスレーショナルリサーチの実際・松山晃文・東大 CRC 講習会・6 月 27 日
3. 再生医療についての行政の取組み・松山晃文・最高裁 再生医療研究会・7 月 3 日
4. iPS 細胞を用いた再生医療の現状と展望・松山晃文・DDS 学会・7 月 4 日
5. 再生医療研究と試薬・松山晃文・日本試薬協会講演会・7 月 9 日
6. 再生医療の動向・松山晃文・再生医療と法研究会・8 月 1 日
7. iPS 細胞で日本は 21 世紀の世界を切り拓く・松山晃文・経営道場・8 月 31 日
8. 再生医療の動向・松山晃文・厚労省全国薬務主管課長会議・9 月 20 日
9. 再生細胞治療と培地・松山晃文・FIRM 講演会・9 月 26 日
10. 非臨床試験 package の提案・松山晃文・MCP 策定会議・10 月 4 日
11. "Development of Regenerative Medicinal Products—From Bench—"・松山晃文・DIA 日本年会・11 月 7 日
12. 臨床薬理に期待すること—再生医療一介の研究者として—・松山晃文・第 34 回臨床薬理学会学術総会・12 月 6 日
13. 再生医療の倫理と規制（2）・松山晃文・東京大学生命倫理講習会・12 月 12 日
14. 臨床研究編臨床応用のための iPS/ES/体性幹細胞の培養について・松山晃文・第 10 回医薬品 RS フォーラム・12 月 14 日
15. 再生医療の動向・松山晃文・東京都薬事監視員協議会・1 月 29 日
16. アカデミアによる開発戦略「再生医療法制定下の医療技術開発」・松山晃文・国立大学附属病院臨床研究推進会議 第 2 回総会シンポジウム・2 月 7 日
17. 幹・前駆細胞の品質管理・松山晃文・3 月 4 日

18. 再生医療とレギュラトリーサイエンス—品質管理の観点から—・松山晃文・第 13 回日本再生医療学会総会　ランチョンセミナー・3 月 4 日
19. “Proposal of the preclinical safety study-pack age for the cell therapy products”・松山晃文・IABS-JST Joint symposium・3 月 7 日
20. ヒト ES/iPS 細胞由来細胞製剤の品質管理・松山晃文・慶応義塾大学生命倫理講習会・3 月 26 日

G. 知的所有権の取得状況

1. 特許取得
「心筋指向細胞」
PCT 出願（平成 25 年 4 月 24 日）
出願人：大阪大学・理化学研究所・（公財）先端医療振興財団
発明者：松山晃文・大倉華雪

2. 実用新案取得
該当なし

3. その他
該当なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

論文

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Matsuyama A.	Translational research in regenerative medicine: A translational gap.	Pharmaceuticals Policy and Law.	15	163-172	2013
Shudo Y, Miyagawa S, Okura H, Fukushima S, Saito A, Kawaguchi N, Matsuura N, Shimizu T, OkanoT, Matsuyama A, Sawa Y.	Addition of mesenchymal stem cells enhances the therapeutic effects of skeletal myoblasyt cell-sheet transplantation in a rat ischemic cardiomyopathy model.	Tissue Eng, part A	20	728-739	2013
Okura H, Soeda M. Miyagawa S, Sawa Y, Ichinose A, Matsuyama A.	reprogrammed spermine treated adipose –tissue-derived multi-lineage progenitor cells improve left ventricular dysfunction in a swine chronic myocardial infarction model.	Proceedings of the 10th International Congress on Coronary Artery Disease.		39-42	2013
Okura H, Soeda M. Morita M, Ichinose A, Matsuyama A.	Transplantation of human adipose tissue-derived multi-lineage progenitor cells but not adipose tissue-derived stromal/stem cells reduces serum cholesterol in hyperlipidemic Watanabe rabbits.	Proceedings of the 10th International Congress on Coronary Artery Disease.		51-54	2013
Okura H, Soeda M. Morita M, Ichinose A, Matsuyama A.	Transplantation of adipose tissue-derived multi-lineage progenitor cells reduces serum cholesterol in hyperlipidemic Watanabe rabbits.	Proceedings of the 10th International Congress on Coronary Artery Disease.		46-51	2013
Moriyama H, Moriyama M, Sawaragi K, Okura H, Ichinose A, Matsuyama A, Hayakawa T.	Tightly regulated and homogeneous transgene expression in human adipose-derived mesenchymal stem cells by lentivirus with tet-off system.	PLoS One.	8	e66274	2013

Kawase R, Ohama T, Matsuyama A, Matsuwaki T, Okada T, Yamashita T, Yuasa-Kawase M, Nakaoka H, Nakatani K, Inagaki M, Tsubakio-Yamamoto K, Masuda D, Nakagawa-Toyama Y, Nishida M, Ohmoto Y, Nishihara M, Komuro I, Yamashita S.	Deletion of progranulin exacerbates atherosclerosis in ApoE knockout mice. Cardiovasc Res.	Cardiovasc Res.	100	125-133	2013
Yuasa-Kawase M, Masuda D, Yamashita T, Kawase R, Nakaoka H, Inagaki M, Nakatani K, Tsubakio-Yamamoto K, Ohama T, Matsuyama A, Nishida M, Ishigami M, Kawamoto T, Komuro I, Yamashita S.	Patients with CD36 Deficiency Are Associated with Enhanced Atherosclerotic Cardiovascular Diseases.	J Atheroscler Thromb.	20	514-515	2013
大倉華雪・松山晃文	細胞医療での申請にあたっての注意点—品質の観点から—	先進医療NAVIGATOR II 再生医療・がん領域の実用化へのTOPICS		5-8	2014
松山晃文	再生医療とレギュラトリーサイエンス -早期実現にむけて合理的な理解を-	ヒューマンサイエンス	7	28-31	2013
松山晃文	再生医療の規制と今後の動向	リーガルマインド	337	36-102	2013
松山晃文	再生医療の早期実現化と国際展開に向けた研究開発支援	再生医療	12	133-134	2013
S Alshammary, Fukushima S , Miyagawa S, Matsuda T, Nishi H, Saito A, Kamata S, Asahara T, Sawa Y.	Impact of cardiac stem cell sheet transplantation on myocardial infarction.	Surg Today	43	970-976	2013
Sawa Y, Miyagawa S.	Present and Future Perspectives on Cell Sheet-Based Myocardial Regeneration Therapy.	Hindawi Publishing Corporation BioMed Research International		1-6	2013

Uchinaka A, Kawaguchi N, Hamada Y, Mori S,Miyagawa S, Saito A, Sawa Y, Matsuura N.	Transplantation of myoblast sheets that secrete the novel peptide SVVYGLR improves cardiac function in failing hearts.	Cardiovascular Research	99	102-110	2013
Shudo Y, Jeffrey E. Cohen, John W. MacArthur, Pavan Atluri, Philip F. Hsiao, Elaine C.Yang, Alexander S. Fairman, Alen Trubelja, Jay Patel, Miyagawa S, Sawa Y, Joseph Woo.	Spatially Oriented, Temporally Sequential Smooth Muscle Cell-Endothelial Progenitor Cell Bi-Level Cell Sheet Neovascularizes Ischemic Myocardium.	Circulation.	128	S59-S68	2013
Fukushima S, Sawa S, Suzuki K.	Choice of cell-delivery route for successful cell transplantation therapy for the heart.	Future Cardiol.	9	215-227	2013
Imanishi Y, Miyagawa S , Fukushima S, Ishimaru K, Sougawa N, Saito A, Sakai Y, Sawa Y.	Sustained-Release Delivery of Prostacyclin Analogue Enhances Bone Marrow-Cell Recruitment and Yields Functional Benefits for Acute Myocardial Infarction in Mice.	PLOS ONE.	8	e69302	2013
Kamata S, Miyagawa S, Fukushima S, Nakatani S, Kawamoto A, Saito A, Harada A, Shimizu T, Daimon T, Okano T, Asahara T, Sawa Y.	Improvement of Cardiac Stem Cell-Sheet Therapy for Chronic Ischemic Injury byAdding ndothelial Progenitor Cell Transplantation: Analysis of Layer-Specific Regional Cardiac Function.	Cognizant Communication Corporation.			2013
Matsuda T, Miyagawa S, Fukushima S, Kitagawa-Sakakida S, Akimaru H, Horii-Komatsu M, Kawamoto A, Saito A, Asahara T, Sawa S.	Human Cardiac Stem Cells With Reduced Notch SignalingShow Enhanced Therapeutic Potential in a Rat Acute Infarction Model.	Circulation Journal	78	222-231	2014
Moriyama M, Moriyama H, Uda J, Matsuyama A,Osawa M,Hayakawa T.	BNIP3 Plays Crucial Roles in the Differentiation and Maintenance of Epidermal Keratinocytes.	Journal of Investigative Dermatology	6	1627-1635	2014

Takayama K, Nagamoto Y, Mimura N, Tashiro K, Sakurai F, Tachibana M, Hayakawa T, Kawabata K, Mizuguchi H.:	Long-Term Self-Renewal of Human ES/iPS-Derived Hepatoblast-like Cells on Human Laminin 111-Coated Dishes.	Stem Cell Reports.	1	322-335	2013
Takayama K, Kawabata K, Nagamoto Y, Inamura M, Ohashi K, Okuno H, Yamaguchi T, Tashiro K, Sakurai F, Hayakawa T, Okano T, Furue MK, Mizuguchi H.	CCAAT/enhancer binding protein-mediated regulation of TGFβ receptor 2 expression determines the hepatoblast fate decision.	Development.	27	91-100	2013
Takayama K, Kawabata K, Nagamoto Y, Kishimoto K, Tashiro K, Sakurai F, Tachibana M, Kanda K, Hayakawa T, Furue MK, Mizuguchi H.	3D spheroid culture of hESC/hiPSC-derived hepatocyte-like cells for drug toxicity testing.	Biomaterials.	34	1781-1789	2013
Kinoshita M, Nakatsuji Y, Suzuki S, Hayakawa T, Kakehi K.:	Quality assurance of monoclonal antibody pharmaceuticals based on their charge variants using microchip isoelectric focusing method.	Journal of Chromatography A	1309	76-83	2013
Iwatsuka K, Watanabe S, Kinoshita M, Kamisue K, Yamada K, Hayakawa T, Suzuki T, Kakehi K.	Free glycans derived from glycoproteins present in human sera.	Journal of Chromatography B	928	16-21	2013
Yodoshi M, Iikeda N, Yamaguchi N, Nagata M, Nishida N, Kakehi K, Hayakawa T, Suzuki S.	A novel condition for capillary electrophoretic analysis of reductively aminated saccharides without removal of excess reagents.	Electrophoresis	34	3198-3205	2013
Kinoshita M, Mitsui Y, Kakoi N, Yamada K, Hayakawa T, Kakehi K.	Common Glycoproteins Expressing Polylactosamine-Type Glycans on Matched Patient Primary and Metastatic Melanoma Cells Show Different Glycan Profiles.	Journal of Proteome Res.	13	1021-1033	2013

Moriyama H, Moriyama M, Isshi H, Ishihara S, Okura H, Ichinose A, Ozawa T, Matsuyama A and Hayakawa T.	Role of Notch signaling in the maintenance of human mesenchymal stem cells under hypoxic conditions.	STEM CELLS & DEV (2014) in press		1-41	2014
森山博由, 森山麻里子, 早川堯夫	ヒト脂肪由来間葉系幹細胞における効率的かつ厳密に発現制御可能なレンチウイルス発現システムの構築	BioMed circus			2013

IV. 研究成果の刊行物・別刷

Pharmaceuticals Policy and Law 15 (2013) 163–172
DOI 10.3233/PPL-130368
IOS Press

Translational research in regenerative medicine: A translational gap

Akifumi Matsuyama*
The Center for Advanced Medical Engineering and Informatics, Osaka University, Osaka, Japan

A medical system is anticipated, where high-quality medical services are accessible without anxieties whenever we are ill. Innovative cell-based regenerative medical/medicinal products, and tissue-engineered medical products, have been used successfully to overcome certain life-threatening diseases, and there is still a need to design/produce more of these products. We translational researchers in regenerative medicine have been trying to translate our scientific findings from bench to bedside. Advanced therapies with cell-based regenerative medical/medicinal products constitute one of the most complex regulatory areas currently approached by clinical research and development in order to generate novel therapeutic applications for patients with incurable disease. We often lack the multidisciplinary skills needed to overcome intricate and complex regulatory tracks and might feel tired from pursuing clinical realization. Basic researchers and clinicians trying to translate stem cell biology into clinical practice might feel defeated by the endless regulatory requirements that apply. In order to help bridge this gap, in this chapter, we review practical issues that must be confronted in order to move from "confidence in mechanism" studies in animals into "proof of concept" studies in human. First, we briefly outline the basic definitions for cell products in the USA, EU and Japan, followed by a focused discussion of the pertinent actions of authorities in Japan.

Keywords: Regenerative medicine, HCT/Ps, cell-based regenerative medical/medicinal products

1. Definition of cell-based regenerative medical/medicinal products

All cell-based regenerative medical/medicinal products aim at same target, but there are some minor differences in their definition among USA, EU and Japan. The cell-based regenerative medicinal products in the USA are included in "Human cells, tissues, or cellular or tissue-based products" (HCT/Ps), which are classified as "biologics", defined in the PHS Act as: any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment or cure of diseases or injuries [FDA Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248; 14 October 1993)].

*Corresponding author: Akifumi Matsuyama, Department of Somatic Stem Cell Therapy and Health Policy, Foundation for Biomedical Research and Innovation, 2-2 Minatojima-minamimachi, Chuo-ku, Kobe, 650-0047, Japan. Tel.: +81 78 304 8706; Fax: +81 78 304 8707; E-mail: akifumi-matsuyama@umin.ac.jp.

HCT/Ps represent articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic scaffold and/or matrix, and semen or other reproductive tissues. As exemption, HCT/Ps that do not meet the following criteria are regulated under the U.S. Food, Drug and Cosmetic: (i) minimal manipulation of the source tissue through the processing stage; (ii) homologous use (i.e., the HCT/P performs the same function(s) in the recipient as the source tissue performed in the donor); (iii) no combination with another article; (iv) lack of intended systemic effect; and (v) no dependence on the metabolic activity of living cells (except in cases of autologous use, use in first- or second- degree blood relatives, or reproductive use) (Public Health Service Act, §361).

In the EU, the cell-based regenerative medicinal products are classified under "advanced therapy medicinal products" (ATMPs), which are divided into three main types: (1) gene therapy, (2) somatic cell therapy, and (3) tissue engineered products [European Directives (2003/63/EC and 2009/120/EC)]. Cells or tissues shall be considered "engineered" if they fulfill at least one of the following conditions: (a) the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement are achieved (Regulation (EC) No. 1394/2007 of the European Parliament and of the Council). For these purposes, the manipulations shall not be considered as substantial manipulations (e.g., cell separation, concentration, or purification); or (b) the cells or tissues are not intended to be used for the same essential function in the recipient as in the donor.

In Japan, the cell-based regenerative medicinal products are classified under "Human cells/tissue-based products" (HCT/Ps). HCT/Ps in Japan meeting criteria for little or no manipulation and same essential function (homologous use) are regulated under the Medical Service Law and Medical Practitioners Law as transplantation or under the Pharmaceutical Affairs Law as blood-infusion. More than minimal-manipulated HCT/Ps shall be regulated under Pharmaceutical Affair's Law in Japan with some exemptions.

2. Cells as medical/medicinal products: Manufacturing aspects

Once we have determined that a particular cellular product lies within the cell-based regenerative medical/medicinal product category, regardless of it being investigational, production of the cells that will be used in human must conform with the good manufacturing practice (GMP) (cGMP, current GMP in USA) for medical/medicinal products (PHS Act, §351.). Patients' safety and law enforcement

should be the primary considerations in advancing medical therapies, GMP implementation should be required if the cell manufacturing processes under GMP substantially increase production costs. It is therefore important that translational researchers of regenerative medicine are aware of the complexities of GMP implementation before starting any translational program based on their basic scientific findings. Typical regulatory concerns surrounding the application of cellular components are product potency and safety, purity and characterization of the cells, and characterization and control of their manufacturing process for quality management. Cell products will usually have to be defined with regard to their identity, purity, potency, stability, and viability.

Potency is interpreted to mean the specific ability or capacity of the product to influence a given result, as indicated by appropriate laboratory examinations or by adequately controlled clinical trials and studies obtained through the administration of the product in the fashion intended. Safety implies the relative freedom from harmful effects to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Thus, with regard to safety, cell donors must be carefully screened and the cellular product, once expanded in the GMP production facilities and equipments through master and/or working cell banks, must be examined using several standardized tests for viability, sterility, endotoxin, adventitious agents, tumorigenicity, pyrogenicity, and mycoplasma infection. Purity means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product and includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

3. Clinical research with cell-based regenerative medical/medicinal products

Before first-in-man clinical trials and studies, both the biological activity and toxicity of the investigational medical/medicinal product must be established in a pertinent animal model according to the good laboratory practice (GLP) (cGLP, current GLP in USA). Unlike for biologics and small molecules, the regulatory pathway for stem cell-derived therapeutics is not well defined and, hence, not well understood. While the biologic and small molecule industries benefit from a well-defined regulatory pathway and commonly abide by practices on preclinical safety testing, product characterization, and measures of purity and potency, the same cannot be said for product development for the stem cell industry. To encourage and to give small to medium size enterprises incentive to conduct quality and nonclinical studies on ATMPs in the EU, the EMA Committee for Advanced Therapies (CAT) has published a related guideline on the minimum quality and nonclinical data required for certification of ATMPs (EMEA/CAT/486831/2008/corr). Even though the certification provided is not legally binding, this system aims at facilitating the evaluation

of any future application for clinical studies and trials and marketing authorization application based on the same data. The stepwise regulatory framework in the EU resembles the non-commercial IND (Investigational New Drug) system applied in the US.

Before starting clinical studies and/or trials, translational investigators must secure the approval of the institutional review boards (IRB) of all institutions involved in the clinical research, in addition to obtaining authorization from the national regulatory authorities of their countries. To guarantee respect for persons, beneficence and justice according to Helsinki Declaration in EU and Japan and Belmont Report in US, good clinical practice (GCP) (cGCP, current GCP in USA) must be followed, in order to ensure data quality, and to avert any avoidable errors and adverse events. Once the authorization and/or approval of the clinical trial and/or study is granted, the sponsor is legally bound to notify the regulatory bodies about any suspected unexpected serious adverse events. The sponsors' duties also include ensuring that there is a health policy in place to cover any liability, that the recruited study subjects have signed appropriate informed consent, and approval of the medicinal products.

4. Post-marketing

This covers approval/authorization, distribution, and pharmacovigilance of cell-based regenerative medical/medicinal products. Confirmation by the regulatory authorities that the quality, safety, and efficacy of a cell-based regenerative medical/medicinal product have been established through successful stepwise clinical phases, is followed by application for marketing authorization and publicization within the healthcare system and health insurance [in the USA, the Health Insurance Portability and Accountability Act (HIP)]. It should be emphasized that continuous surveillance of the safety of the investigational medical/medicinal products and post-marketing pharmacovigilance are key issues in all translational research on cell-based regenerative medical/medicinal products. These products are often considered relatively "high risk" and regulatory bodies will require tight safety follow-up of all patients treated with cell-based regenerative medical/medicinal products, both in clinical trials and postmarketing sales.

5. Publicization within the healthcare system and health insurance

As mentioned above, the regulatory authorities are acting with caution when approving cell-based regenerative medical/medicinal products. At this stage, the healthcare and/or health insurance providers have yet to determine whether healthcare reforms will allow them to benefit from regenerative therapies, which are likely to require many years to accrue sufficient savings to cover upfront costs. We translational researchers should publicize the rapid advances in the field, reproducible

results in clinical trials, and the ever increasing therapeutic benefits of the new products.

Any approach can be viable if two major hurdles are overcome commercially: total costs of manufacturing the product, quality control, shipping and administration costs, and significant benefits for the patients and societies. As providers perform more critical health economic analyses in decision-making, truly potent or disease-modifying therapies will offer greater value than conventional ones. While we still do not know whether regenerative medicine will provide niche benefit or will revolutionize healthcare, cell-based regenerative medical therapies invite us to this goal, although the efficacy of the currently approved products have been limited compared with standardized care, particularly as related to the costs of cell-based therapies relative to the cost of standard of care.

6. How to fill the translational gap

The development of cell-based medical/medicinal products, from bench to bedside, is a long, costly, highly regulated, and high-risk process. As such, it is difficult to develop such products and achieve a reasonable success rate in marketing, and thus support should be sought from the multinational pharmaceutical companies, with their large financial and human resources, to develop new medical/medicinal products. Unfortunately, however, translational research in regenerative medicine has so far attracted relatively little interest from the pharmaceutical industry. The reasons are general uncertainties with regard to the therapeutic promise of cell-based regenerative medical/medicinal products, high production and quality control costs, and extreme logistical complexity related to the specific characteristics of these products, such as their generally short shelf life, relatively long-term investment commitment before any financial return, and the existence of different international regulatory environment. It is therefore obligatory to exercise some sort of translation between promising basic scientific findings and the pharmaceutical industries.

The pharmaceutical and biotechnology companies have recently taken an increased interest in regenerative medicine *in vitro*. The use of stem cells as drug screening and research tools has grown with most of the major pharmaceutical companies are using embryonic stem cells or adult stem cells for intramural drug discovery/screening portfolios. Here, rather than focus on the extensive application of the technology as tools for drug development, we should discuss the emerging opportunities for biopharmaceutical companies in engaging in stem cell-based regenerative medicine. This could include their involvement in research and development projects on the production of novel small- and large-size molecule therapeutics designed to steer endogenous stem cell fate to the desired cells, or in projects aimed at stimulating autologous and/or allogeneic somatic stem cells and tissue regeneration, typically via the actions of paracrine factors, i.e., the cytokine effects. Of course one should

not forget also the ultimate promise of stem cell research, i.e., that of cell/tissue replacement therapy (or *in situ* stem cell therapy). Cell replacement therapies are not far-fetched but a reality based on the fact that stem cell derivatives can accurately recapitulate the normal function of cells or tissues and restore function in diseased organs/tissues. Based on the above, we encourage the pharmaceutical industry to participate both logistically and financially in our efforts of establishing new stem cell-based therapies, palliative therapy, disease modification and in *in situ* stem cell therapy, in addition to their role in drug manufacturing.

In the absence of well-defined regulatory requirements for the development and approval of more than minimal manipulated stem cell therapeutics, it is necessary to have expertise on collaborative work to deal with the concerns of the regulatory bodies on bench research. The knowledge base for new developments in stem cell research generally resides in the academic research community, small- to medium-size biotechnology companies with substantial research capacity, and those well connected to academic research teams. The individual academic scientists are generally less well prepared for the highly regulated aspects of product development and management with timeline and milestone, particularly those related to toxicological testing, consistency, and source of product as required for GTP handling and GMP manufacturing. In many cases, the academic researchers are less familiar with the project and/or product management demands of the industry, where delays in product development are very costly, not only to the investors but potentially to the patients, who you like to be cured. Thus, there is clearly a potential for cooperation between academic research resources and the know-how of the industries.

7. Two independent regulatory frameworks for cell-based regenerative medical/medicinal products in Japan

As mentioned, the EMA Committee for CAT has published a related guideline on the minimum quality and nonclinical data required for certification of ATMPs. In addition they have released hospital exemptions. In this regard, the FDA has given IND for non-commercial first-in-man clinical trials with minimum quality and non-clinical data for certification and orphan drug application as special categories (Fig. 1). The Japanese government has a similar regulatory framework requiring minimum quality and non-clinical data for certification in EU and US. The track in Japan to translate cell-based medical/medicinal products from bench to bedside has been regulated under the Medical Service Law and the Medical Practitioner's Law but not under the Pharmaceutical Affair's Law, and the guideline is "The guideline for clinical research using human stem cells" (Fig. 2).

The Japanese Government have encouraged studies on the plasticity of stem cells. However, to diminish uneasiness about safety, many questions remain to be resolved. On this account, it is important to develop guidelines on this matter that researchers, including research organizations, can follow appropriately in clinical