After *Myriad*, what types of claim amendments change a patent ineligible isolated gene claim into an eligible patent claim that is 'markedly different' from Nature?

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A new empirical study examines the types of claim amendments that have successfully transformed isolated gene (nucleic acid) claims from *ineligible subject matter* into patent *eligible* inventions to the satisfaction of USPTO patent examiners. It provides further clarity into the threshold of subject-matter eligibility for gene-related patents and answers outstanding questions related to claim drafting practice after *Myriad*.

While nearly four years have passed since the US Supreme Court's decision in *AMP v Myriad*, its impact is still not fully understood. The Supreme Court held that "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring"[1]. The decision left open many questions and was "far from illuminating"[2]. The United States Patent & Trademark Office (USPTO) subsequently published updated Examination Guidance on patent eligible subject matter every year since 2014 (refs. 3, 4, 5). This Guidance comments upon and gives examples of eligible and ineligible claims after *Myriad*[1], *Mayo*[6] and *Alice*[7], but the Guidance has not settled debates[8]. Some believe that the *Myriad* decision will have a profound effect on the genomics industry and biotech innovation[9]. At the opposite end of the spectrum, some commentators believe that the *Myriad* decision is of little practical importance because "patent attorneys are developing strategies to 'draft around' *Myriad* and related cases to ensure their client patents will withstand scrutiny going forward"[10].

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Still others argue that the impact of *Myriad* remains uncertain[11] because, even considering USPTO Guidelines and the Supreme Court decision, there is considerable on-going legal debate about the criteria for eligible gene patents and what makes a claim 'markedly different' from ineligible natural products[12,13,8].

In a recently published empirical study[14], we addressed questions about *Myriad's* impact on *gene-related* patents (including but not limited to isolated gene-related patents). That study employed an automated search algorithm designed to analyze, in a broad way, *Myriad's* impact by looking at granted gene-related patents using consistent search terms before and after the *Myriad* decision.

The empirical results in our previous study indicated that the *Myriad* ruling on subject-matter eligibility had indeed affected gene-related patenting, but in a less profound way than had been predicted by some authors prior to the Supreme Court decision. Instead, the results empirically confirmed more moderate predictions of impact such as those made by Graff *et al*[15]. However, despite being able to analyze the large scale impact by looking at general patenting trends, automated patent search methodologies have intrinsic limitations that prevented us from providing conclusive answers to important questions about how gene-related patent claims are changing after *Myriad*. In particular, methodologies based on automated search algorithms are typically not suitable to answer detailed *claim-related* questions such as what types of claims, claim amendments, and legal arguments in originally published *isolated nucleic acid* patent applications are resulting in allowable subject-matter after examination proceedings by the USPTO. Consequently, manual claim analysis is needed to address currently unanswered questions of significant practical and legal importance. These include: is it *really* possible to draft around *Myriad* and obtain claims with equal (or very similar) scope?[10,13,16]; or has the decision driven patent applicants towards narrower claims?[17]; what types of claim amendments have been successfully applied to transform ineligible *isolated* nucleic acid claims into patent eligible claims in examination proceedings before the USPTO?; and, relatedly, has *Myriad* failed to provide a workable legal test of subject matter eligibility?[18]. The answers to these questions are also important in debates addressing whether *Myriad* has caused a problem such that 35 USC 101 should be amended[19, 20].

Our research also highlights the operation of the USPTO Manual of Patent Examination Procedure (MPEP) and Examination Guidelines,[5] and raises questions about the quasi-legal influence of the USPTO *qua* administrative agency on the innovation ecosystem[21]. How is the USPTO applying its own Examination Guidelines in this area? This in turn casts light on whether future litigation in the courts will confirm or reject the

USPTO's interpretation of *Myriad,* potentially invalidating newly issued patents several years from now.

In an effort to help resolve legal and business uncertainty, we have devised a method (inspired by other claim level empirical studies[22]) that identifies and systematises concrete *post-Myriad* examples of recently granted gene patents which were applied for with at least one isolated nucleic acid claim. These concrete empirical examples highlight what the USPTO considers to make a claim 'markedly different' from naturally-occurring genomic DNA (gDNA).

In the instant study we focussed on answering the following three empirically-based research questions: 1) what proportion of human gene-related patent applications published during the 3-year period preceding *Myriad* contain an *isolated nucleic acid* product claim (i.e., a claim similar to the isolated gDNA claim in contention in *Myriad*)?; 2) what proportion of these applications (with at least one isolated nucleic acid product claim) matured into a granted patent; and 3) how were simple isolated nucleic acid claims that received a *Myriad*-based rejection amended to become patent eligible subject matter before the USPTO?

Methods

A. Search Strategy & Inclusion Criteria

Our study is based on patent applications that were published by the USPTO in the three-year period preceding the *Myriad* ruling (i.e., US patent applications published from 2010-06-13 to 2013-06-13). Furthermore, we restricted our study to applications with biological claims directed to "Homo sapiens." A search algorithm (**S1, Supplementary Information**) was applied in the online, publicly available Lens patent resource[23,24] This search algorithm (**Figure 1** Step 1) is designed to identify patent applications with at least one claim containing a SEQ ID and the keyword *isolated* within 5 words of *nucleic acid* (and synonyms of nucleic acid). The algorithm was intended as a pre-processing step prior to manual expert claim review, and consequently it was designed to optimize its *sensitivity* to isolated nucleic acid patents as opposed to its *specificity,* since specificity is subsequently achieved through expert manual claim review[25].

The effect of this inclusion criteria was that we identified a cohort of applications with relevant claims that were published before the *Myriad* ruling. We were then able to identify a subset of these applications that were examined after *Myriad*, at which point the applicant and USPTO would need to consider carefully the legal arguments and amendments required for the isolated nucleic acid claims to meet patent eligibility after *Myriad.*

B. Patent Application Classification

The output of the automated search algorithm (**S1**) was used as the input for the first step in the expert claim review and manual classification (**Figure 1 Steps 2-4**). These steps involved manually analyzing the claims in each of the applications retrieved and classifying them as containing either: 1) at least one *simple isolated genomic nucleic acid product claim* (i.e., claims akin to those litigated in *Myriad*) (**M1a**)*;* 2) no M1a-satisfying claims but at least one claim to more *complex isolated nucleic acids* (e.g., isolated nucleic acids in vectors, or sequences coding for monoclonal antibodies) (**M1b**); or 3) neither M1-satisfying nor M1b-satisfying claims but *broad gene-related claims* (e.g., polypeptides encoded by specific nucleic acid sequences (**M1c)**. Our definition of simple isolated genomic nucleic acid product claims is similar to that adopted in *Graff et al.*[15]*,* except our definition does not include claims that are limited only to cDNA or recombinant nucleic acids. Applications with only complex isolated nucleic acid claims (**M1b**) and broad gene-related claims (**M1c**) were excluded from this study. The remainder of our study looked at what happened to the **M1a** applications; these are the applications that one would expect to be most directly affected by the reasoning in *Myriad.*

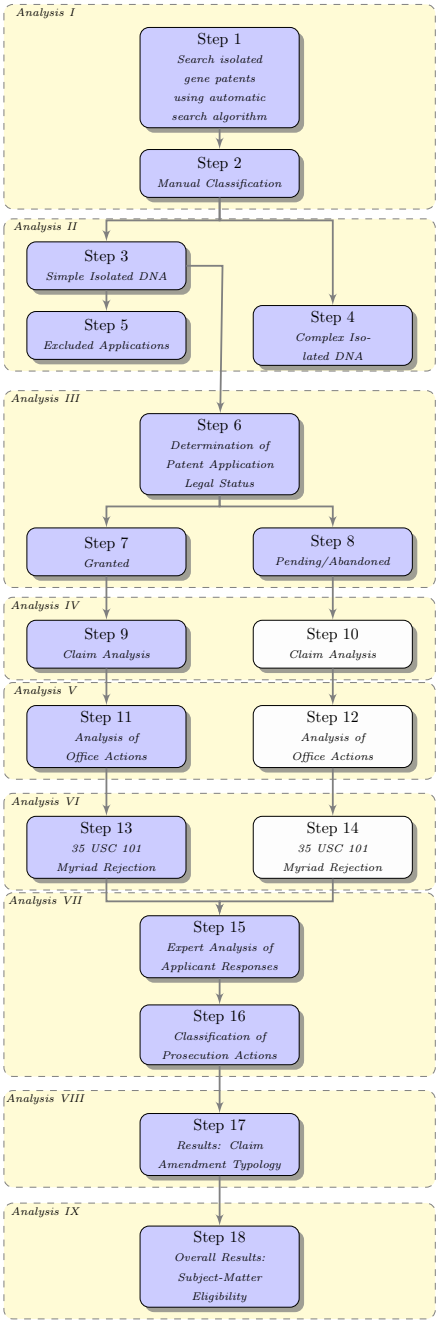

Figure 1 Methodological overview including the automated search, manual classification, and expert prosecution history review steps.

C. Patent Application Prosecution History Review

The prosecution histories of the applications (commonly known as 'file wrappers') with simple isolated genomic nucleic acid claims were obtained from the USPTO Patent Application Information Retrieval System (PAIR) in January 2017. At that time, we determined the legal status of the patent applications and sub-classified them into either 1) Granted (**M1aG**); 2) Rejected/abandoned (**M1aR**), or 3) Pending (**M1aP**) (**Figure 1 Steps 6-8)**. The remaining steps in our method looked closely at the **M1aG** patents to see what happened during their prosecution that enabled them to be granted notwithstanding that when initially published they included at least one simple isolated genomic nucleic acid product claim, and the fact that many of these claims issued after the *Myriad* ruling held such claims to be patent ineligible.

The patent file wrappers were further examined in order to determine if the originally submitted claims had been amended prior to examination on the merits (**Figure 1 Step 9**). This involved expert review of the prosecution history to identify any preliminary amendments where the applicant canceled the isolated nucleic acid claims prior to examination on the merits or where the isolated gene claims were withdrawn from consideration in response to a USPTO Restriction Requirement where the applicant elected the non-isolated gene claims (e.g., method claims, systems claims, etc) for examination on the merits. Amendments were classified as occurring either: (i) prior to examination on the merits, meaning the amendment was applicant-initiated prior to the Patent Examiner issuing an Office Action addressing the patentability of the claimed invention (**M1aGA1**); (ii) in response to a USPTO Restriction Requirement (**M1aGA2**); or (iii) in response to an Office Action during examination on the merits (**M1aGA3**). The patent applications classified as **M1aGA3** were of most interest in this study because the file wrappers record the Examiner's specific rejections and objections, including *Myriad*-based (35 USC 101 subject matter eligibility) rejections, and the arguments and specific claim amendments the Applicant made in response to the Office Actions in order to overcome the rejections of record.

We also studied the timing for discontinuation of the simple isolated nucleic acid product claims in **M1aGR** (**Figure 1 Step 11**). For example, some but not all of the isolated nucleic acid product claims in **M1aGR** were discontinued in response to examination on the merits (**M1aGRC3**). Indeed, some were discontinued by the applicant prior to examination on the merits (**M1aGRC1**), and sometimes discontinuation (claim withdrawal) was in response to a USPTO Restriction Requirement (**M1aGRC2**) meaning that the examiner took the view that the application involved more than one invention to be searched, and only one invention could be taken forward for examination with the patent application. Many applicants of M1aG patent applications elected to take forward non-isolated nucleic acid claims (e.g., method claims, systems claims, etc) for examination on the merits after a Restriction Requirement.

The next step in the analysis involved conducting an expert review of the USPTO Office Actions (Non-Final Rejections, Final Rejections), Examiner Interview Summaries, and Advisory Actions (**Figure 1 Steps 11,13,15**). Each patent application was coded to indicate whether it received a 35 USC 101 (subject matter eligibility) *Myriad*-based rejection (**Figure 1 Step 13**). Each Applicant's Response to a Non-Final Office Action, Final Office Action, Advisory Action, Examiner Interview Summaries, and Appeal Briefs was also reviewed (**Figure 1 Step 15**). This enabled us to observe how many applications received *Myriad*-based rejections, and to analyze claim amendments and legal arguments that overcame them (**Figure 1 Step 16)**. The **Supplementary Information** provides further details about the methodology and coding notation used in this study.

D. Claim Amendment Typology

The results of the Analysis I-VII in **Figure 1** were used to establish a typology of claim amendments which overcame *Myriad*-based rejections (**Figure 1 Step 17).** This typology thus shows the sorts of claim amendments that transformed *ineligible* simple isolated nucleic acid claims into patent eligible inventions after the *Myriad* ruling to the satisfaction of USPTO Examiners.

Results & Discussion

A. Answers to Research Questions

Table 1 shows the primary results from this study. The goal of this study was to help answer three particular questions related to *Myriad's* impact at the claim level. With regards to the first question, we found 653 applications with at least one simple isolated genomic nucleic acid product claim. This constitutes approximately 50% of the 1292 human gene-related applications found by our S1 search algorithm.

The second question was directed to finding out the proportion of the 653 applications that were eventually granted. In other words how many of these patent applications 'made it' notwithstanding *Myriad?* Our results show that 313 (47.9%) applications were eventually granted (**M1aG**), 311 (47.6%) were wholly rejected/abandoned (**M1aR**) (meaning all claims discontinued), and 29 (4.4%) were, ats of January 2017, pending (**M1aP**).

We then looked more closely at the **M1aG** subset (n=313). We wanted to see how these patents had managed to survive the *Myriad* ruling. Of these, 183 applications (58.5%) advanced prosecution to allowance by surrendering (i.e., canceling) all simple isolated nucleic acid products claims (**M1aGC**). These patents, when finally granted, no longer contained any of the isolated nucleic acid claims which had been published prior to the *Myriad* decision. The **M1aGC** cohort, taken together with the **M1aR** applications

(where the simple isolated nucleic acid claims were abandoned or rejected along with every other claim), reveal that a very large proportion of *Myriad*-type claims filed in the three years before *Myriad* were not taken forward by applicants (79.2% of the 653 in the **M1a** subset). We discuss the significance of this result along with our view that this may be time-dependant and the result of legal uncertainty below.

We found only 14 (4.5%) applications were granted without substantive amendments to the originally published isolated nucleic acid claims (**M1aGU**). Significantly, all but one of these were examined on the merits before the *Myriad* decision. Some of these claims are now at risk of invalidation in light of *Myriad,* but some of these claims may still be valid if they are limited to nucleic acids that do not exist in nature. In any event, the **M1aGU** subset is small, constituting approximately 1% of the 1292 applications identified in our **S1** search algorithm.

Question 3 asked how did the isolated nucleic acid product claims that received a *Myriad*-based rejection change during prosecution in order to become, according to the corresponding USPTO Examiner, patent eligible? We found 116 (37.1% of M1aG) instances where simple isolated nucleic acid product claims were amended (but not canceled) during prosecution (M1aGA). Of these, we found 21 patent applications with simple isolated genomic nucleic acid product claims that were amended in response to an explicit *Myriad*-based rejection (in the other cases Applicants amended their claims prior to receiving an Office Action or the Examination on the Merits occurred before the *Myriad* decision). These patent applications with explicit *Myriad* rejections are of special interest because they record specific communication between the USPTO and Applicants who successfully prosecuted *Myriad*-type claims, including details of the amendments (and legal arguments) that were ultimately successful.

Table 1 Results of isolated DNA Patent Claim Analysis

S1-Results of Automated Patent Search Algorithm	1292	
Manual Classification (M1 Analysis)	N	Pct
M1a-Simple Isolated DNA	653	50.5%
M1b-Complex Isolated DNA	561	43.4%
M1c-Excluded	78	6.0%
Total	**1292**	100%
Patent Status Review of M1a Applications (Isolated DNA)	N	Pct M1a
M1aG-Granted	313	47.9%
M1aR-Rejected/Abandoned	311	47.6%
M1aP-Pending	29	4.4%
M1a Total	**653**	100%
Patent Claim Analysis of M1aG Applications (Granted)	N	Pct M1aG
M1aGC-Isolated Gene Claims Canceled	183	58.5%
M1aGA-Isolated Gene Claims Amended	116	37.1%
M1aGU-Isolated Gene Claims Unchanged	14	4.5%
M1aG Total	**313**	100%
Fate of Isolated-DNA Related Patents (Granted & Abandoned)	N	Pct M1a
Rejected/Abandoned Patent Application (Canceled All Claims)[M1aR]	311	49.8%
Canceled Isolated Gene Claims [M1aGC]	183	29.3%
a) Total Cancelled (Application or Isolated Gene Claims) [M1aR+M1aGC]	**494**	79.2%
b) Amended Isolated Gene Claims	**116**	18.6%
c) Granted as Originally Filed (Unchanged)	**14**	2.2%

We created a typology to classify the amendments that, after *Myriad,* successfully transformed a simple isolated nucleic acid product claim into a patent-eligible claim. Aside from cancelling the isolated nucleic acid claims (n=183), the typology reveals that applicants are typically employing one of eight prosecution strategies: 1) amending to cDNA; 2) amending to nucleic acids with non-naturally occurring sequence variations; 3) amending to nucleic acids recombinantly linked with heterologous sequences; 4) amending to labelled nucleic acids; 5) amending to a nucleic acid in a vector; 6) amending to a nucleic acid recombined with a non-specific regulatory sequence; 7) amending with a Type-2 change and a negative-claim clause; and 8) amending to a short nucleic acid (so short that it does not naturally occur).

The **Supplementary Information** provides definitions for each of these strategies and details the amendments made in each of the 21 cases, including some of the arguments made by Applicants and Examiners. This Information also records three applications that received a *Myriad*-based rejection and, as a result, the Applicants cancelled the claims.

The most common way to amend and overcome a *Myriad*-based rejection was to claim cDNA, which occurred in seven of these 21 instances. As described below, although some of these eight strategies may appear obvious in hindsight, the concrete examples provide additional guidance on what degree of difference satisfies

the USPTO that an isolated nucleic acid product claim is markedly different from those in nature.

B. Is it Easy to Draft Around *Myriad*?
Our results indicate that in the years immediately after *Myriad* there has been much less amending activity than some commentators had expected. In over 79.2% of **M1a** cases the simple isolated nucleic acid product claims were canceled. Claim amendments were attempted and successful in less than 18.6% of the cases. We found only 21 (3.2% of the **M1a**) instances of successful amendments after receiving an explicit *Myriad* rejection. Furthermore, in none of these cases involving successful amendments, is the scope (breadth) of the granted claims equivalent to the original scope.

When we commenced this study we expected to see more amending activity to overcome *Myriad* rejections; we did not expect so many cancellation of entire patents nor so many canceled claims which excised a nucleic acid claim without any attempt to amend the claim to closely related subject-matter eligible claims. There were potentially many reasons for the large proportion of discontinued isolated nucleic acid product claims. Undoubtedly one reason was the view that such claims were ineligible and difficult to draft around after *Myriad*. No guidelines were initially issued, and even then detailed information for addressing *Myriad*-based rejections in relation to isolated nucleic acids was unavailable. There were also reasons other than patent eligibility, for example, concerns about novelty, obviousness or unity of invention. Another explanation is that such claims are simply not as valuable as they were once perceived to be and are suffering a "Darwinian fate"[26].

It is important to note that canceled *Myriad*-type claims could, in some cases, be resurrected and amended in future, claiming the original priority date; for example as a divisional, continuation or continuation-in-part patent application. So it may be that some applicants that discontinued *Myriad*-type claims are waiting to learn more about successful claim-drafting practices before trying to prosecute or amend contentious *Myriad*-type claims. The typology, information and concrete examples in this study of what works and doesn't work is the sort of information that patent practitioners may find helpful. In particular, the file wrappers disclose important nuances that applicants have only learnt through trial and error.

For example, in one of the 21 applications to receive a *Myriad*-based rejection, the applicant attempted to overcome the rejection by claiming an 'isolated polydexoyriboneculeotide that, when transcribed and translated, yields a *polypeptide* [that exists in nature]'. However, the examiner maintained the rejection and suggested that the claim be amended to cDNA instead; the applicant accepted this amendment (Case #1, Supplementary Information). In another application that received a *Myriad*-based rejection, the applicant amended a *Myriad*-type claim to 'synthetic DNA'; however, the examiner maintained the rejection because the claim still included a sequence that existed in nature despite being made in a synthetic, unnatural way (Case #7, Supplementary Information). In yet another example, an examiner rejected a claim limited to 'designer' nucleic acids because it was not clear how the nucleic acids differed from those in nature. The examiner in this case even said that it is common for experts in the field to "describe natural processes of evolution as examples of 'engineering' or 'design'". The applicant eventually overcame the rejection by claiming specific, non-naturally occurring sequences (Case #11, Supplementary Information).

Based on these results, we can conclude that, to date, applicants have not found techniques to draft-around *Myriad* to obtain claims of equal breadth to isolated nucleic acid claims. However, some applicants have been able to amend ineligible isolated nucleic acid claims so that the resulting subject-mater eligible claims lie close to the boundary stated in *Myriad* between ineligible and eligible subject matter. Also we cannot go so far as to say that drafting around *Myriad* to achieve equal breadth is impossible: successful strategies might be found in claims that were, for example, amended for reasons unrelated to subject matter, or that occurred before examination on the merits.

In the immediate aftermath of the *Myriad* ruling, it may turn out that applicants have avoided trying to draft around *Myriad* (preferring instead to cancel the claims) because there is not enough of a business case to warrant this effort. Or it may turn out that applicants have delayed doing so due to current legal uncertainty. This will be clearer in a few years when we can see if a significant number of the canceled *Myriad*-type claims are resurrected as continuations or divisionals, and successfully amended at that point in time.

C. What is 'Markedly Different' from Nature after *Myriad*?
In the *Myriad/Mayo* Examination Guidance published between 2014 and 2016, the USPTO provides just a few concrete examples to demarcate when a claim directed to a nucleic acid has markedly different characteristics from naturally occurring nucleic acids. The primary Guidance published in the Federal Register on Dec 16, 2014 (ref. 3) states that markedly different characteristics may be found in chemical or physical structure, biological or pharmacological function, chemical or physical properties, functional or structural characteristics, or other properties. Alongside this general information, the Federal Register gives one example (ref 3, ibid, p 74625-6): i) a claim to an exons-only cDNA, where the naturally occurring gDNA also includes introns. On the same day (outside the Federal Register), three further examples were issued by the USPTO (ref. 3 Guidance issued on Dec 16, 2014 titled 'Nature-based product examples 9-18') to explain where a claim

directed to a nucleic acid is markedly different: ii) the claimed nucleic acid includes a non-naturally occurring nucleic acid substitution; iii) the claimed nucleic acid includes a non-naturally occurring fluorescent label; iv) the claim is to a non-natural combination of vector and nucleic acid[8].

Our results found seven examples in the **M1a** subset where an applicant successfully amended a claim so that it was directed to cDNA. This type of claim amendment was not surprising in view of it being explicitly mentioned in the Supreme Court opinion and the *Myriad/Mayo* Interim Examination Guidance of 2014. Nevertheless this type of amendment to overcome the *Myriad* product of nature exclusion remains controversial[2]; the apex court in Australia held, in a parallel *Myriad* case, that cDNA is not patent eligible subject matter[27].

Our analysis of the file wrappers also sheds further light on how claims to cDNA must be drafted to comply with *Myriad*. In one instance, an applicant attempted to overcome a *Myriad*-based rejection by claiming a "complementary DNA sequence." The examiner maintained their rejection because a "complementary DNA sequence" could be interpreted as "any DNA sequence that is complementary to some other sequence" (Case #14, Supplementary Information). By contrast, in a different example, a claim to 'complementary nucleic acid (cDNA)' was sufficient to overcome a *Myriad*-based rejection (Case #2, Supplementary Information). The difference between these examples is that the second explicitly includes the term of art "cDNA," as opposed to the more general concept of complementarity.

We found five successful amendments which reached grant by including non-naturally occurring nucleic acid variations. We also found two examples where amending a claim to include a combination of label and nucleic acid successfully transformed a claim that had been challenged pursuant to *Myriad*.

We found one example where the applicant amended the claim so that it was a non-natural combination of vector and nucleic acid.

Some of these amendment types were predictable if one takes into account the non-Federal Register *Myriad/Mayo* Guidance 2014; however, this Guidance was not issued until 18 months after *Myriad*. Moreover, we also observed some important nuances in the arguments raised and accepted by USPTO Examiners about what did and did not amount to 'markedly different characteristics' in cases of amendments directed to sequence variations and labels, even where the Guidance indicated that the characteristics were likely to be considered markedly different. For instance, an isolated nucleic acid that was amended to comprise "at least one modified nucleotide for increased nuclease resistance" was rejected because the claim still included naturally-occurring nucleic acids. Eventually, the applicant amended to claim specific isolated nucleic acids which have moieties that confer nuclease resistance (and do not occur in nature) (Case #10, Supplementary Information). In another example, an amendment that limited a *Myriad*-type claim to instances when the "single stranded nucleic acid is labeled" was rejected because it was not significantly different from that which exists in nature. Ultimately, the applicant overcame the rejection by specifying that "the single stranded nucleic acid is labeled '*with a dye*'" (Case #16, Supplementary Information).

Beyond the Examination Guidance, we found four additional strategies which applicants used to successfully respond to *Myriad*-based rejections. These are described as Types 3, 5, 7, and 8 in the **Supplementary Information**. Amending to claim recombinant nucleic acids (Types 3 and 5) is perhaps an obvious strategy in light of *Myriad;* however, we observed important nuances that must be adhered to here as well. For example: an amendment that merely limited a claim to "recombinant" nucleic acids was rejected because the claim did not encompass nucleic acids that are markedly different from those in nature. A nucleic acid made by recombination does not necessarily differ in structure or function from from a naturally occurring nucleic acid (Case #13, Supplementary Information). An amendment that linked an isolated nucleic acid to a promoter was also rejected because it is "well-known that various promoters and enhancers are present in the human genome …" (Case #24, Supplementary Information).

D. What has been the Response of the USPTO to *Myriad*?

Our results show that the USPTO implemented the *Myriad* ruling swiftly. We found examples where patent applications had received Notices of Allowance in the three months preceding the *Myriad* ruling (i.e., examination on the merits had concluded) but were stopped from issuance and prosecution reopened with a *Myriad*-based rejection (e.g., Cases #7 and #24, Supplementary Information). In general, our results also indicate the USPTO Examiners are interpreting *Myriad* and USPTO Examination Guidance literally and narrowly; though it is still debatable whether they are giving effect to the Supreme Court's statement that differences should be 'marked.' For example, does limiting the claim to a single "molecule that includes a nucleic acid and a fluorescent label" really constitute a "marked difference" from *Nature*?

We also found that Examiners are conservative in their use of discretion and do not tend to grant allowances based on claim language that deviates from the specific examples provided in the Examination Guidance. The strict attitude is reinforced by the USPTO's current practice of not granting patents on isolated naturally-occurring polypeptides (Case #12 Supplementary Information). Although the position against eligibility is conservative overall, there seems to be inter-examiner variability. For example, an

oligonucleotide that did not differ to sequences in nature was granted (Case #21, Supplementary Information), yet a claim to a pair of primers was rejected (Case #23, Supplementary Information).

The conservative approach of USPTO Examiners probably results in longer prosecution-times and in some cases patent applicants may be surrendering *more* patent protection scope than needed in order to satisfy the Examiners with regards to 35 USC 101 requirements (depending on one's view of the requirement for a 'marked difference' rather than a mere 'difference' from naturally occurring nucleic acid). If so, a potential positive side effect is that granted patents are more likely to withstand a validity challenge, should one be made via the courts at a future time. On balance it is unclear whether the conservative approach is beneficial. The longer patent prosecution times could disproportionately affect startups and small firms. They may not have the resources for engaging in this type of complex prosecutions involving multiple rounds of examination and RCEs (Requests for Continued Examination), unlike larger firms with more resources. We found some preliminary evidence of such disproportionate effect in our previous empirical study[14]. Strong, reliable patents are typically important for businesses which need 1) to attract investment in a risky R&D environment, and 2) firm growth during the term of the patent (ie., 20 years from the filing date). But strong, reliable patents are particularly important for SMEs. These firms are important providers of disruptive innovation (e.g., new ventures; substitute and new entrant products), which often require a period of market protection to challenge incumbents. In contrast, larger firms tend to dominate continuous improvement (or sustained-innovation) and can rely more on existing capital, marketing, brand recognition, R&D budgets, and existing distribution channels for competitive advantage.

Assuming the USPTO's interpretation is correct, the information in this paper offers examples of successful claims amendments that could help applicants with their pending patent prosecutions in this technical field. Relatedly, next time a landmark case like *Myriad* is decided, we suggest that the relevant patent office should endeavour to produce updated guidelines quickly and with as much detail as possible.

Conclusions & Further Research

It is important to emphasize that our empirical results involving claim amendments focus on USPTO examination of human gene-related claims in applications receiving a *Myriad* rejection that were examined in the last three years. Based on these results, we conclude that there has been no successful "drafting around" the legal principles in *Myriad* to the point of achieving protection of equal breadth to isolated gDNA claims. There has been some claim drafting to achieve claims that sail close to the boundary between eligible and ineligible subject matter, and there is still some room for debate whether applicants are being issued claims that are different from nucleic acid, but not *markedly* different. In contrast to the limited drafting around activity, many applicants advanced prosecution of their applications containing isolated nucleic acid product claims by cancelling the *Myriad*-type claims during the election process or during examination.

In so far as patent practitioners did engage with claim amendments after a *Myriad*-based rejection from a USPTO Examiner, applicants primarily claimed cDNA; the eligibility of which was explicitly affirmed by the US Supreme Court in *Myriad* and the primary *Myriad/Mayo/Alice* guidance from the USPTO. Other allowable amendments followed other examples in the 2014 USPTO Guidance[5], namely sequence variations, labelling, and nucleic acids inserted into vector. USPTO Examiners were noticeably conservative with what they considered acceptable amendments in these categories. We observed a handful of other amendments - not currently mentioned in USPTO Examination Guidelines - which successfully shifted a simple isolated nucleic product claim from ineligible to eligible subject matter. These are interesting additions to "the patent practitioners' tool box."

In terms of further research, one might conduct manual claims analysis of the **M1b** cohort (patents filed with at least one complex isolated nucleic acid claim) and the **Ma1GA1** and **Ma1GA2** (patents filed with at least one simple isolated nucleic acid claim that were granted after amending the claim during the election process or via preliminary amendment) to see if any additional strategies for drafting around *Myriad* emerge. Another insightful line of enquiry would be to investigate the US family members related to the M1a subset. Such follow-on research could help answer, for instance, whether the *Myriad*-type claims that were cancelled in the uncertain aftermath of *Myriad* are being resurrected and filed as 'children' applications (applications claiming the priority benefit of an earlier application) as the threshold of patent eligibility and business value of nucleic acid patents becomes clearer. In addition to examining the US patent families, another topic ripe for further research is to examine patent family members in other jurisdictions, especially family members filed with the the European Patent Office (EPO). Empirical answers to these questions would help provide further insight into the debate regarding the effects of having divergent patent eligibility requirements in this important technical field across jurisdictions.

Our prediction is that studies like this, further debate, additional USPTO Guidance, future court decisions —in short, the passage of time—will resolve some of the uncertainty that still surrounds the *Myriad* distinction between ineligible claims directed to products of Nature, and eligible claims that have 'markedly different characteristics'[12]. In turn, we think it is

possible that the dominant prosecution and claim amendment strategies in this field may change in the future. For instance, applicants that cancelled *Myriad*-type claims in the aftermath of *Myriad*, may in time decide to amend the claim in a manner which becomes predictably likely to succeed. At that time they can file a divisional, continuation or continuation-in-part application claiming the priority benefit to the older co-pending applications and still obtain some protection for these product claims. However, whether we see this dynamism and time-dependency with claim drafting will also depend upon whether the cancelled, potentially amendable claims are perceived as having economic value. It is also a separate question whether developments in claim-drafting, sailing increasingly closer to the boundary of *Myriad*, are beneficial for scientific research and innovation.

In summary, based on the nuances that we observed in amendments that satisfy current USPTO practice, we would conclude in the immediate aftermath of *Myriad* it has not been necessarily easy for applicants to draft *Myriad*-compliant amendments that obtain the broadest claim scope available, particularly if exclusivity over a cDNA sequence is not a valuable right. However, applicants need not abandon *in toto* their *Myriad*-type claims if one sees good reason for pursuing related amended nucleic acid claims. As shown by this study, there are more than half a dozen tried-and-tested claim drafting strategies that can transform ineligible simple isolated nucleic acid product claims into USPTO eligible claims after *Myriad*. We hope that this study and prosecution examples will help provide further clarity and practical insight into the emerging USPTO threshold for subject-matter eligibility for gene-related patents. One of the key issues that the various stakeholders (e.g., biotech researchers, inventors, entrepreneurs, investors, business, and patent practitioners) agree on is the need for at at least a reasonable degree of legal certainty in order to promote efficiency in genomic research, investment, and innovation, which requires clarity and predictability for the scope of the patent rights in this IP intensive field.

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Supplementary Information

Patent Search Algorithm (S1)

a) Search Strategy: claims:((seq id) AND ("isolated DNA"~5 OR "isolated gene"~5 OR "isolated nucleotide"~5 OR "isolated (deoxyribonucleic acid)"~5 OR "isolated (nucleic acid)"~5))
b) Dates: 2010-06-13 to 2013-06-13
c) Database: Lens.org;
d) Jurisdiction: USA (USPTO);
e) Biologicals: Homo Sapiens

Patent Application Coding Schema

M1a = Simple Isolated DNA
M1aG = Simple Isolated DNA Granted
M1aR = Simple Isolated DNA Rejected/Abandoned
M1aP = Simple Isolated DNA Pending
M1aGA = Simple Isolated DNA Granted Claims Amended
M1aGC = Simple Isolated DNA Granted Claims Cancelled
M1aGU = Simple Isolated DNA Granted Claims Unchanged

Amendment Type
M1aGA1 = Simple Isolated DNA Granted Amended - Preliminary Amendment
M1aGA2 = Simple Isolated DNA Granted Amended - Response to Election/Restriction - Election
M1aGA3 = Simple Isolated DNA Granted Amended - Response to Office Action
M1aGA4 = Simple Isolated DNA Granted Amended - Appeal

Cancelation Type
M1aGC1 = Simple Isolated DNA Cancelled - Preliminary Amendment
M1aGC2 = Simple Isolated DNA Cancelled - Withdrawn in Response to Election/Restriction - Election
M1aGC3 = Simple Isolated DNA Cancelled - Response to Office Action
M1aGC4 = Simple Isolated DNA Cancelled - Appeal

Myriad Rejections
M1aGAxM1 = M1a Granted Claims (any Type) with 35 USC 101 Myriad-Type Rejection
M1aGAxM2 = M1a Granted Claims Amended without 35 USC 101 Myriad-Type Rejection
M1aGAxM2a = M1a Granted Claims Amended without 35 USC 101 Myriad-Type Rejection (after Myriad)
M1aGAxM2b = M1a Granted Claims Amended without 35 USC 101 Myriad-Type Rejection (before Myriad)
M1aGCxM2a = M1a Granted Claims Cancelled without 35 USC 101 Myriad- Rejection (after Myriad)
M1aGCxM2b = M1a Granted Claims Cancelled without 35 USC 101 Myriad-Type Rejection (before Myriad)
M1aGUxM2a = M1a Granted Claims Unchanged without 35 USC 101 Myriad-Type Rejection (after Myriad)
M1aGUxM2b = M1a Granted Claims Unchanged without 35 USC 101 Myriad-Type Rejection (before Myriad)

Pivoting point for granted: date of issuance.

Illustrative Example(s):
Example 1: **M1aGA3M1** indicates a patent application containing at least one product claim directed to **simple** isolated DNA, that was **granted**, and that the isolated DNA claim was **amended** in **response** to an Office Action during **examination of the merits**, and the Office Action **included** a 35 USC 101 **Myriad-**type rejection

Example 2: **M1aGC2M2a** indicates a patent application containing at least one product claim directed to simple isolated DNA, that was granted, and that the isolated DNA claim was cancelled in response to an a Restriction requirement (i.e., the claim was not elected -withdrawn from consideration- and later cancelled) and the Office Actions (at least one provided after the Myriad Supreme Court ruling) did **NOT** a 35 USC 101 Myriad-type rejection (because the claim had already been cancelled.

Amendments due to *Myriad*-based Rejections: Published Application Claims v Granted Claims

Please note:

- Words in the granted claims highlighted in yellow indicate the elements of the claim that were amended to comply with the *Myriad*-based rejection.
- The dates used below refer to the date stamp given to the documents by the USPTO, the dates may not correspond to the dates in which the correspondence was sent or received.
- Where possible, the claim numbers used below correspond to the ones on Lens.com

Summary of Amendments:

Type 1: cDNA – 7
Type 2: Nucleic acid with non-naturally occurring sequence variations – 5
Type 3: Heterologous Recombination - 3
Type 4: Label – 2
Type 5: Recombination with non-specific regulatory nucleic acid – 1
Type 6: Vector – 1
Type 7: Type 2 and a negative-claim clause – 1
Type 8: Short nucleotide – 1
Type 9: Cancelled – 3 (183 total cancelations)

Description of Amendment Classifications:

1. *cDNA* – The amendment meant that only cDNA was claimed.
2. *Nucleic acid with non-naturally occurring sequence variations* – The amendment meant that only nucleic acids with non-naturally sequence variations were claimed.
3. *Heterologous Recombination* – The amendment meant that only nucleic acids linked to sequences from different species were claimed.
4. *Label* – The amendment meant only labelled nucleic acids were claimed.
5. *Recombination with non-specific regulatory nucleic acid* – The amendment meant that only a nucleic acid sequence linked to a non-specific regulatory nucleic acid was claimed.
6. *Vector* – The amendment meant that only a nucleic acid in a vector was claimed.
7. *Type 2 and a negative-claim clause* (*Nucleic acid with non-naturally occurring sequence variations; and a negative-claim clause)* – The amendment meant that only nucleic acids with non-naturally occurring variant(s) were claimed. In addition, the claim specifies that the claimed sequences are no not identical or complementary to all or a portion of other naturally occurring DNA.
8. *Short nucleic acid* – The amendment meant that only a short nucleic acid was claimed.
9. *Cancelled* – The claims were cancelled.

PATENTS

Type 1: cDNA

1. Title: Pregnancy-associated Plasma Protein-a2 (papp-a2) Polynucleotides

Application Publication No: 2013/0095569 A1
Application No: 13/625,088
Relevant Claim:

1. An isolated polynucleotide encoding a polypeptide that
(a) consists of mature PAPP-A2 (amino acid residues 234-1791 of SEQ ID NO:2); or
(b) is at least 95% identical to the polypeptide of (a), and differs from the polypeptide of (a) solely by
(i) deletion of 1-10 amino acid residues from, or addition of 1-10 residues to, the amino terminal, and/or
(ii) deletion of 1-10 residues from, or addition of 1-10 residues to, the carboxy terminal, and/or
(iii) one or more conservative substitutions;
wherein said polypeptide has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5).

Grant Publication No: 9005949 B2
Relevant Grant Claim:

1. A cDNA that encodes a polypeptide that
(a) consists of amino acid residues 234-1791 of SEQ ID NO: 2 (mature pregnancy associated plasma protein A2 (PAPP-A2)); or
(b) is at least 95% sequence identical to the polypeptide of (a), and differs from the polypeptide of (a) solely by
(i) deletion of 1-10 amino acid residues from, or addition of 1-10 residues to, the amino terminal, and/or
(ii) deletion of 1-10 amino acid residues from, or addition of 1-10 residues to, the carboxy terminal, and/or
(iii) one or more conservative substitutions;
wherein said polypeptide has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5).

Amendment type: cDNA

Notes: The applicant initially attempted to make the claim patent eligible by claiming an isolated "polydeoxyribonucleotide" instead of a "polynucleotide", arguing that the claim "no longer read on naturally occurring nucleic acids…". This amendment and argument was, however, rejected (non-final rejection 15 August 2014). The applicant then amended the claim to read "An isolated polydeoxyribonucleotide that, when transcribed and translated yields a polypeptide"… (Response after final action, 13 November 2014). Eventually, after an applicant-initiated interview, the claim was drafted to cDNA (11 December 2014).

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2. Title: Mammalian Alpha-kinase Proteins, Nucleic Acids And Diagnostic And Therapeutic Uses Thereof

Application Publication No: 2013/0011919 A1
Application No: 12/803,001
Relevant Claim:

1. An isolated nucleic acid encoding mammalian melanoma alpha kinase, wherein the nucleic acid is selected from the group consisting of:
a. the DNA sequence of SEQ ID NO: 28;
b. the DNA sequence of SEQ ID NO: 26;
c. DNA sequences that hybridize to the sequence of subparts (a) or (b) under standard hybridization conditions; and
d. DNA sequences capable of encoding the amino acid sequence encoded by the DNA sequences of subparts (a), (b) or (c).

Grant Publication No: US8916379 B2
Relevant Grant Claim:

1. A complementary nucleic acid (cDNA) encoding mammalian melanoma alpha kinase having alpha kinase activity, wherein the nucleic acid is selected from the group consisting of
a. SEQ ID NO: 26; and
b. cDNA sequences capable of encoding the amino acid sequence encoded by SEQ ID NO:27.

Amendment type: cDNA

Notes: The examiner initially raised the *Myriad*-based rejection in an examiner-initiated interview (28 February 2014), which was then repeated in a non-final rejection (28 February 2014).

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3. Title: Use Of Novel Cytokine Receptors As Biomarkers And Therapeutic Targets In Human Cancer

Application Publication No: 2012/0329065 A1
Application No: 13/595,436
Relevant Claim:

1. An isolated nucleic acid selected from the group consisting of a nucleic acid encoding erythropoietin receptor isoform 5 and having the sequence given herein as SEQ ID NO: 12; a nucleic acid that encodes the opposite strand of a nucleic acid of SEQ ID NO: 12.

Grant Publication No: 8617844 B2
Relevant Grant Claim:

1. An isolated nucleic acid selected from the group consisting of a cDNA acid encoding erythropoietin receptor isoform 5 and having the sequence given herein as SEQ ID NO: 12; a cDNA is the full length complement of SEQ ID NO: 12

Amendment type: cDNA

Notes: The *Myriad*-based rejection was raised during an examiner-initiated interview (2 December 2013). This interview actually took place *after* a notice of allowance was issued (6 June 2013). During the interview the applicant authorised the claim amendment above. This amendment, however, didn't make it to the granted patent until a certification of correction was issued (28 October 2014).

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4. Title: Identification And Use Of Genes Encoding Amatoxin And Phallotoxin

Application Publication No: 2010/0267019 A1
Application No: 12/268,22
Relevant Claim:

1. An isolated nucleic acid sequence comprising at least one sequence set forth in SEQ ID NOs:1-4, 55-56, 79-81, 85-86, and 95-96.

Grant Publication No: 9518097 B2
Relevant Grant Claim:

1. A nucleic acid consisting essentially of one of the sequences set forth in SEQ ID NOs: 55, 56, or 79.

Amendment type: cDNA

Notes: These SEQ ID NOs list cDNA sequences (see applicant arguments, 4 June 2014).

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5. Title: Identification Of A Novel Bhd Gene

Application Publication No: 2011/0288031 A1
Application No: 13/179,853
Relevant Claim:

14. An isolated nucleic acid molecule encoding the polypeptide of claim 1, wherein the molecule hybridizes with a nucleic acid probe comprising the sequence shown in SEQ ID NO: 1 under wash conditions of 55° C., 1.0×SSC for 30 minutes.

(Claim 1: A purified folliculin polypeptide: having an amino acid sequence comprising the sequence set forth in SEQ ID NO: 2; having an amino acid sequence comprising a sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO: 2; encoded by a nucleic acid molecule comprising the sequence set forth in SEQ ID NO: 42; or encoded by a nucleic acid molecule comprising a sequence having at least 90% sequence identity to the sequence set forth in SEQ ID NO: 42.)

Grant Publication No: 8865880 B2
Relevant Grant Claim:

1. An isolated cDNA molecule consisting of a nucleic acid sequence encoding a polypeptide: having an amino acid sequence consisting of the sequence of SEQ ID NO: 2; having an amino acid sequence consisting of a sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 2; wherein the isolated cDNA molecule hybridizes with a nucleic acid probe comprising the sequence shown in SEQ ID NO: 1 under wash conditions of 55° C., 1.0×SSC for 20 minutes.)

Amendment type: cDNA

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6. Title: Mutation Of The Parkin Gene, Compositions, Methods And Uses

Application Publication No: 2012/0064598 A1

Application No: 13/209,495
Relevant Claim:

1. An isolated nucleic acid molecule encoding a human parkin, comprising a DNA sequence of SEQ ID NO:1 with at least one genetic alteration comprising
   a) a deletion of one or more exons, in combination or otherwise,
   b) a multiplication of exons,
   c) a point mutation,
   d) a deletion of 1 or more contiguous base pairs,
   e) an insertion of 1 or more contiguous base pairs or
   f) a combination thereof.

Grant Publication No: 8835618 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule encoding a human parkin comprising a cDNA sequence of SEQ ID NO:1 with at least one genetic alteration comprising:

a) a deletion of one or more exons selected from the group consisting of: exon 2, exons 2-3, exons 2-4, exons 3-4, exons 3-6, exons 3-9, exon 5, exons 5-6, exon 6, exons 6-7, exons 7-9, and exon 8;
b) a multiplication of exons selected from the group consisting of:
a triplication of exon 2,
a duplication of exon 3,
a duplication of exon 6,
a duplication of exon 7,
and a duplication of exon 11;
c) a point mutation selected from the group consisting of:
a mutation from adenine to thymine at position 584,
a mutation from guanine to adenine at position 601,
a mutation from adenine to thymine at position 734,
a mutation from cytosine to thymine at position 867,
a mutation from thymine to adenine at position 905,
a mutation from cytosine to thymine at position 924,
a mutation from guanine to adenine at position 939,
a mutation from thymine to guanine at position 966,
a mutation from guanine to adenine at position 1084,
a mutation from cytosine to thymine at position 1101,
a mutation from guanine to cytosine at position 1239,
a mutation from guanine to adenine at position 1281,
a mutation from cytosine to adenine at position 1345,
a mutation from guanine to adenine at position 1390, and
a mutation from guanine to adenine at position 1459;
d) a deletion of 1 or more contiguous base pairs selected from the group consisting of:
a deletion of nucleotides adenine and guanine at positions 202-203,
a deletion of adenine at position 255, and
a deletion of nucleotides guanine and adenine at positions 1142-1143; or
e) an insertion of 1 or more contiguous base pairs selected from the group consisting of: an insertion of guanine and thymine at positions 321-322.

Amendment type: cDNA

7. Title: Tryptophanyl-trna Synthetase-derived Polypeptides Useful For The Regulation Of Angiogenesis

Application Publication No: 2012/0238620 A1
Application No:
Relevant Claim:

1. An isolated nucleic acid encoding a polypeptide capable of inhibiting angiogenesis or neovascularization, wherein the nucleic acid comprises a first polynucleotide sequence comprising a coding sequence at least 95 percent identical to a sequence selected from the group consisting of SEQ ID NO:6, a polynucleotide sequence that encodes a polypeptide of SEQ ID NO:12, and a polynucleotide sequence that encodes a fragment of the polypeptide of SEQ ID NO:12; and wherein the nucleic acid does not encode for the amino acid sequence of amino acids 71-93 of SEQ ID NO:1.

Grant Publication No: 8796237 B2
Relevant Grant Claim:

1. An isolated cDNA encoding a polypeptide or a fragment of the polypeptide capable of inhibiting angiogenesis or neovascularization, wherein the isolated cDNA comprises a first polynucleotide sequence comprising a coding sequence at least 95 percent identical to a sequence selected from the group consisting of SEQ ID NO:6, a polynucleotide sequence that encodes a polypeptide of SEQ ID NO:12, and a polynucleotide sequence that encodes a fragment of the polypeptide of SEQ ID NO:12.

Amendment type: cDNA

Note: A notice of allowance was issued on application claim 1 in a slightly modified version to that above (notice of allowance, 3 April 2013). However, this notification was withdrawn due to reconsideration of the patents in light of *Myriad* (notice of withdrawal from issue, 27 November 2013). After a telephone interview with the examiner, the applicant amended the introductory phrase of the claim to "An isolated DNA selected form the group consisting of cDNA, recombinant hybrid DNA and synthetic DNA…" (claims 14 November 2013). This amendment was rejected because no "hybrid DNA" was disclosed and "synthetic DNA" has the same sequence as that which exists in nature (non-final rejection 19 December 2013). Subsequently, the applicant limited the claim to cDNA (applicant arguments, 30 January 2014).

Type 2: Nucleic acid with non-naturally occurring sequence variations

8. Title: Ssx-2 Peptides Presented By Hla Class Ii Molecules

Application Publication No: 2011/0144186 A1
Application No: 12/028,953
Relevant Claim:

1. An isolated nucleic acid molecule encoding an SSX-2 HLA class II-binding peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

Grant Publication No: 920047 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule encoding an SSX-2 HLA class II-binding peptide comprising an endosomal targeting signal, wherein the SSX2 HLA class II-binding peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: The examiner raised the *Myriad*-based rejections in an examiner-initiated interview (19 March 2015) and then again in a non-final rejection (20 March 2015). The examiner advised that the amendments above would be eligible at the interview and in the non-final rejection because the naturally-occurring version of the protein does not ordinarily have the endosomal targeting signal (non-final rejection 20 March 2015). The applicant adopted these amendment in the next version of the claims (19 June 2015).

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9. Title: Variant Activin Receptor Polypeptides

Application Publication No: 2011/0183897 A1
Application No: 13/080,515
Relevant Claim:

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:
(a) a polynucleotide having sequence set forth in the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96 or its complement; and
(b) a polynucleotide encoding a polypeptide having the amino acid sequences set forth in the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97.

Grant Publication No: 8716459 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:
(a) a polynucleotide having sequence set forth in SEQ ID NO 23;
(b) a polynucleotide encoding a polypeptide having the amino acid sequences set forth in SEQ ID NO: 24;

(c) a polynucleotide encoding a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence set forth at amino acids 25 through 134 of SEQ ID NO:18, wherein the polypeptide comprises an amino acid substitution at position 28 of SEQ ID NO:18;
(d) a polynucleotide encoding a polypeptide comprising an amino acid sequence at least 98% identical to the amino acid sequence set forth at amino acids 25 through 134 of SEQ ID NO:18, wherein the polypeptide comprises an amino acid substitution at position 28 of SEQ ID NO:18; and
(e) a polynucleotide encoding a polypeptide comprising an amino acid sequence at least 99% identical to the amino acid sequence set forth at amino acids 25 through 134 of SEQ ID NO:18, wherein the polypeptide comprises an amino acid substitution at position 28 of SEQ ID NO:18.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: Each isolated nucleic acid molecule listed includes non-naturally-occurring modifications). For a discussion on the modifications see, applicant arguments (23 December 2013).

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10. Title: Dna Virus Microrna And Methods For Inhibiting Same

Application Publication No: 2012/0070892 A1
Application No: 13/307,694
Relevant Claim:

1. An isolated nucleic acid Epstein Barr virus (EBV) microRNA molecule having a maximum of 50 nucleotides comprising any one of SEQ ID NOS: 1 and 3-5.

Grant Publication No: 9476048 B2
Relevant Grant Claim:

1. An isolated nucleic acid Epstein Barr virus (EBV) microRNA molecule having a maximum of 50 nucleotides comprising a sequence selected from the group consisting of SEQ ID NOS: 1 and 3-5, wherein at least one ribonucleotide in said sequence is modified to confer nuclease resistance as compared to the unmodified naturally occurring microRNA, and wherein the modification of the ribonucleotide is selected from the group consisting of a C_1 to C_4 alkyl group substituted at the 2′ position, a C_1 to C_4 alkoxy-C_1 to C_4 alkyl group substituted at the 2′ position, and a methylene bridge between the 2′-oxygen atom and the 4′-carbon atom.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: The applicant attempted to overcome the *Myriad*-based rejection by amending the claim to state that the isolated nucleic acid "molecule comprises at least one modified nucleotide for increased nuclease resistance" (applicant arguments, 10 March 2014). This amendment was, however, rejected for being too broad because it included amendments that were naturally occurring and were already published (final rejection, 2 July 2014). The applicant again tried to overcome the *Myriad*-based rejection by stating that the isolated nucleic acid had been "*chemically* modified" for increased nuclease resistance (applicant arguments, 2 October 2014). This second amendment was rejected because some chemical alterations can result in amendments which are identical to those that exist in nature (non-

final rejection, 30 October 2014). Finally, the applicant amended the claim to read, "wherein the sequence comprises at least one chemical modified ribonucleotide having a moiety which confers nuclease resistance (applicant arguments, 30 January 2015). This amendment was sufficient to overcome the *Myriad*-based rejection, but additional amendments were required for other reasons.

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11. Title: Transcription Activator-like Effectors

Application Publication No: 2012/0270273 A1
Application No: 13/353,662
Relevant Claim:

1. A nucleic acid molecule encoding a designer transcription activator-like effector (dTALE) polypeptide, the nucleic acid molecule comprising a sequence encoding a nucleic acid binding domain and one or more mammalian effector domains, wherein the sequence encoding the nucleic acid binding domain comprises sequences encoding two or more monomer units arranged in a predetermined 5′ to 3′ order, wherein each said monomer unit comprises a variable disresidue that specifically binds a target nucleotide, and wherein the nucleic acid binding domain encoded by the nucleic acid molecule specifically binds a predetermined nucleic acid sequence, and wherein each one or more mammalian effector domains encoded by the nucleic acid molecule mediates an effector function.

Grant Publication No: 9499592 B2
Relevant Grant Claim:

1. A nucleic acid molecule encoding a designer transcription activator-like effector (dTALE) polypeptide fragment, the nucleic acid molecule comprising a sequence encoding a nucleic acid binding domain of the dTALE polypeptide fragment and one or more mammalian effector domains, wherein the sequence encoding the nucleic acid binding domain comprises a sequence encoding two or more monomer units arranged in a predetermined 5′ to 3′ non-endogenous TALE order,
wherein each said monomer unit comprises a variable diresidue that is capable of specifically binding a target nucleotide,
wherein the nucleic acid binding domain encoded by the nucleic acid molecule is capable of specifically binding a predetermined target nucleic acid sequence,
wherein each of the one or more mammalian effector domains encoded by the nucleic acid molecule is capable of mediating an effector function, and
wherein the nucleic acid molecule further comprises an expression vector comprising the sequence of an expression vector of SEQ ID NOs: 192-195.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: Although the application claim detailed "a designer transcription activator-like effector" the examiner rejected this claim under *Myriad* because the claim "did not set forth specific structural properties of the claimed nucleic acids that make it clear the nucleic acids are non-naturally occurring." (non-final rejection 2 October 2014). The applicant amended the claim to give a little more detail on the invention (2 April 2014), but the examiner maintained that nucleic acids listed could be found in nature. Furthermore, the examiner stated that it is common for people skilled in the art "to make reference to the 'arrangement' of domains in naturally occurring proteins and to describe naturally processes of evolution as examples of 'engineering' or 'design'. (final rejection, 19 May 2015). The applicant

eventually made the claim patent eligible by making the amendment above (applicant arguments 10 November 2015).

The additional clause "wherein the nucleic acid molecule further comprises an expression vector comprising the sequence of an expression vector of SEQ ID NOs: 192-195" was actually added due to a 102 rejection (applicant arguments, 20 June 2016).

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12. Title: Immunogenic Peptides And Methods Of Use

Application Publication No: 2011/0165117 A1
Application No: 13/025,094
Relevant Claim:

> 17. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 16.
>
> (Claim 16: An isolated polypeptide comprising at most ten consecutive amino acids of the amino acid sequence set forth as (SEQ ID NO: 1)MSARVRSRSRGRGDGX$_1$X$_2$APDVVAFVAPGESQQEEPPTDNQDIEPGQER EGTPPIEERKX$_3$X$_4$GDCQEMDX$_5$EKTRSERGDGSDVKEX$_6$X$_7$PPNPKHX$_8$ KTKE AGDGQP wherein X1 is Q or Y, X2 is E or L, X3 is V or Y, X4 is E or L, X5 is V or L, X6 is K or Y, X7 is T or L, and X8 is A or V and wherein the polypeptide comprises one of
> (a) amino acids 16 to 25 of SEQ ID NO: 1, wherein amino acid X$_1$ is a glutamine and amino acid X$_2$ is a glutamic acid;
> (b) amino acids 59 to 68 of SEQ ID NO: 1, wherein amino acid X$_3$ is a valine and amino acid, X$_4$ is a glutamic acid and X$_5$ is a valine; or
> (c) amino acids 84 to 92 of SEQ ID NO: 1 wherein the amino acid X$_6$ is a leucine, amino acid X$_7$ is a threonine and amino acid X$_8$ is a alanine.)

Grant Publication No: 9175057 B2
Relevant Grant Claim:

> 14. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 13.
>
> (Claim 13. A polypeptide consisting of amino acids 59 to 68 of SEQ ID NO: 1(X$_3$X$_4$GDCQEMDX$_5$), wherein amino acid X$_3$ is a valine, amino acid X$_4$ is a glutamic acid, and amino acid X$_5$ is a valine.)

Nucleic acid with non-naturally occurring sequence variations

Notes: The examiner rejected amendments to the polypeptide claim because they encompassed naturally occurring sequences of amino acids (see, non-final rejection, 9 January 2015).

Type 3: Heterologous recombination

13. Title: Genes Encoding A Novel Type Of Lysophophatidylcholine Acyltransferases And Their Use To Increase Triacylglycerol Production And/or Modify Fatty Acid Composition

Application Publication No: US2013/0152230 A1
Application No: 13/745,257
Relevant Claim:

1. A nucleic acid molecule, wherein said nucleic molecule is isolated, purified or recombinant, and comprises the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34.

Grant Publication No: 9228175 B2
Relevant Grant Claim:

1. A nucleic acid molecule comprising a first polynucleotide operably linked to a second, heterologous polynucleotide, wherein the first polynucleotide encodes at least one peptide selected from the group consisting of SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, and SEQ ID NO:84.

Amendment type: Heterologous recombination

Notes: The initial *Myriad*-based rejection stated that the recombinant nucleic acid molecules claimed were not eligible subject matter because there was no "indication that the recombinant nucleic acids have any characteristics (structural, functional, or otherwise) that are different from naturally occurring nucleic acids." (non-final rejection 22 May 2015).

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14. Title: Smndelta7 Degron: Novel Compositions And Methods Of Use

Application Publication No: 2012/0322852 A1
Application No: 13/510,149
Relevant Claim:

1. An isolated nucleic acid comprising a nucleic acid sequence encoding a SMNΔ7 degron, wherein said nucleic acid sequence is SEQ ID NO. 3 or SEQ ID NO. 14.

Grant Publication No: 8993741 B2
Relevant Grant Claim

1. An isolated nucleic acid encoding a chimeric polypeptide comprising a degradation signal sequence and a target sequence, wherein the degradation signal sequence consists of SEQ ID NO. 3 or SEQ ID NO. 14.

Amendment type: Heterologous recombination

Notes: The examiner raised the *Myriad*-based rejection in a non-final rejection (4 November 2013). The applicant attempt to make the claim patent eligible by claiming a "complementary

DNA sequence" instead of an "isolated nucleic acid" (applicant's amendments (27 January 2014). This amendment, however, was rejected because, as drafted in the claim, a "complementary DNA sequence" could be interpreted as "any DNA sequence that is complementary to some other sequence", not as a cDNA molecule that was deemed patent eligible in *Myriad* (final rejection, 24 February 2014). The amendment above was made in response to this rejection.

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15. Title: Use Of Regulatory Sequences For Specific, Transient Expression In Neuronal Determined Cells

Application Publication No: 2011/0016547 A1
Application No: 12/894,766
Relevant Claim:

1. A DNA segment comprising a regulatory sequence isolated free of the complete DCX gene protein coding region, wherein the regulatory sequence comprises a regulatory sequence selected from the group consisting of:
(a) regulatory sequences comprising the nucleotide sequence shown in SEQ ID NO: 1, as shown in SEQ ID NO: 2, as shown in SEQ ID NO: 3 or as shown in SEQ ID NO: 4;
(b) regulatory sequences comprising the nucleotide sequence contained in the insertion of clone DSM 15111 and obtainable by amplification using two oligonucleotides having the sequences indicated under SEQ ID NO: 9 and SEQ ID NO: 10;
(c) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 1 from position 1166 to 1746, from position 1166 to 2049, from position 1785 to 1843 or from position 1953 to 2775;
(d) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 2 from position 529 to 1079, from position 529 to 1390, from position 1118 to 1175 or from position 1291 to 2137;
(e) regulatory sequences comprising at least a functional part of a sequence of (a) to (d) and causing specific expression in neuronal determined cells;
(f) regulatory sequences comprising a nucleotide sequence which is at least 75% identical to a sequence as defined in (a) to (d) or which comprises a nucleotide sequence which is at least 78% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1166 to 1746 or from position 1166 to 2049 or to the nucleotide sequence shown in SEQ ID NO: 2 from position 529 to 1079 or from position 529 to 1390, which comprises a nucleotide sequence which is at least 82% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1785 to 1843 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1118 to 1175 or which comprises a nucleotide sequence which is at least 75% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1953 to 2775 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1291 to 2137; and
(g) regulating sequences comprising a nucleotide sequence which hybridizes with a complementary strand of the regulatory sequence as defined in (a) to (f) for the early, transient expression of a heterologous nucleotide sequence in proliferative neuronal determined cells

Grant Publication No: 8841430 B2
Relevant Grant Claim:

1. A DNA segment comprising a regulatory sequence and a heterologous nucleic acid molecule that is to be expressed and which originates from a different genetic context than said regulatory sequence, the heterologous nucleotide sequence being operatively linked to said regulatory sequence, said regulatory sequence being selected from the group consisting of:
(a) regulatory sequences comprising the nucleotide sequence shown in SEQ ID NO: 1, as shown in SEQ ID NO: 2, as shown in SEQ ID NO: 3 or as shown in SEQ ID NO: 4;
(b) regulatory sequences comprising the nucleotide sequence contained in the insertion of clone DSM 15111 and obtainable by amplification using two oligonucleotides having the sequences indicated under SEQ ID NO: 9 and SEQ ID NO: 10;
(c) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 1 from position 1166 to 1746, from position 1166 to 2049, from position 1785 to 1843 or from position 1953 to 2775;
(d) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 2 from position 529 to 1079, from position 529 to 1390, from position 1118 to 1175 or from position 1291 to 2137;
(e) regulatory sequences comprising a nucleotide sequence which is at least 75% identical to a sequence as defined in (a) to (d) or which comprises a nucleotide sequence which is at least 78% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1166 to 1746 or from position 1166 to 2049 or to the nucleotide sequence shown in SEQ ID NO: 2 from position 529 to 1079 or from position 529 to 1390, which comprises a nucleotide sequence which is at least 82% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1785 to 1843 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1118 to 1175 or which comprises a nucleotide sequence which is at least 75% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1953 to 2775 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1291 to 2137; and
(f) regulatory sequences comprising a nucleotide sequence which hybridizes under stringent conditions with a complementary strand of the regulatory sequence as defined in (a) to (e) and which provides early, transient expression of a heterologous nucleotide sequence in proliferative neuronal determined cells.

Amendment type: Heterologous recombination

Type 4: Label

16. Title: Forensic Identification

Application Publication No: 2013/0144047 A1
Application No: 13/761,648
Relevant Claim:

1. An isolated single stranded nucleic add consisting of a sequence selected from: SEQ ID NO 1TCTA TCTG TCTA $(TCTG)_4$ $(TCTA)_3$-; SEQ ID NO 2TCTA $(TCTG)_4$ $(TCTA)_7$-; SEQ ID NO 3$(TCTA)_2$ $(TCTG)_4$ $(TCTA)_3$, TCCA $(TCTA)_3$-; SEQ ID NO 4$(TCAT)_4$ CAT $(TCAT)_7$ TCGT TCAT-; SEQ ID NO 7$(T'T'TC)_3$ T'T'T' T'TCT $(CT'T')_5$ T $(CT'T')_3$ CTCC $(T'TCC)_2$-; SEQ ID NO 8$(T'T'TC)_3$ T'T'T' T'TCT $(CT'T')_{13}$ CCT'T $(CT'T')_5$ CTCC $(T'TCC)_2$-; SEQ ID NO 9$(T'T'TC)_3$ T'T'T' T'TCT $(CT'T')_{16}$ CCT'T $(CT'T')_5$ CTCC $(T'TCC)_2$-; SEQ ID NO 10$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_{15}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 11$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_{16}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 12$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_{17}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 13$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_8$ $(CTGT)_4$ $(CT'T')_{13}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 14$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_8$ $(CTGT)_5$ $(CT'T')_{13}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 15$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_{11}$ $(CTG'T')_3$ $(CT'T')_{14}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 16$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_{10}$ $(CTCT)_5$ $(CT'T')_{13}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 17$(T'T'TC)_4$ T'T'T' T'T $(CT'T')_{12}$ $(CTG'T')_5$ $(CT'T')_{14}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 18$(T'T'TC)_2$ T'T'T' T'T $(CT'T')_{14}$ $(CTGT)_3$ $(CT'T')_{14}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 19$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA (TCTA)2 TCCATA $(TCTA)_6$ TCGTCT-; SEQ ID NO 20$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_9$ TCGTCT-; SEQ ID NO 21$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_2$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{10}$ TCGTCT-; SEQ ID NO 22$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_8$ TCGTCT-; SEQ ID NO 23$(TCTA)_5$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_9$ TCGTCT-; SEQ ID NO 24$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{10}$ TCGTCT-; SEQ ID NO 25$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TCGTCT-; SEQ ID NO 26$(TCTA)_6$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TCGTCT-; SEQ ID NO 27$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 28$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TA TCTA TCGTCT-; SEQ ID NO 29$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TA TCTA TCGTCT-; SEQ ID NO 30$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{13}$ TA TCTA TCGTCT-; SEQ ID NO 31$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{14}$ TATCTA TCGTCT-; SEQ ID NO 32$(TCTA)_{10}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 33$(TCTA)_{11}$ $(TCTGT)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 34$(TCTA)_{11}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA

(TCTA)$_{13}$ TCGTCT; SEQ ID NO 35(TCTA)$_{13}$ (TCTG)$_5$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{12}$ TCGTCT; and SEQ. ID NO: 36(AGAA)$_8$-.

Grant Publication No: 8940484 B2

Relevant Grant Claim:

1. An isolated single stranded nucleic acid consisting of a sequence selected from: SEQ ID NO 1TCTA TCTG TCTA (TCTG)$_4$ (TCTA)$_3$-; SEQ ID NO 2TCTA (TCTG)$_4$ (TCTA)$_7$-; SEQ ID NO 3(TCTA)$_2$ (TCTG)$_4$ (TCTA)$_3$, TCCA (TCTA)$_3$-; SEQ ID NO 4(TCAT)$_4$ CAT (TCAT)$_7$ TCGT TCAT-; SEQ ID NO 7(TTTC)$_3$ TTTT TTCT (CTTT)$_5$ T (CTTT)$_3$ CTCC (TTCC)$_2$-; SEQ ID NO 8(TTTC)$_3$ TTTT TTCT (CTTT)$_{13}$ CCTT (CTTT)$_5$ CTCC (TTCC)$_2$-; SEQ ID NO 9(TTTC)$_3$ TTTT TTCT (CTTT)$_{16}$ CCTT (CTTT)$_5$ CTCC (TTCC)$_2$-; SEQ ID NO 10(TTTC)$_4$ TTTT TT (CTTT)$_{15}$ (CTTC)$_3$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 11(TTTC)$_4$ TTTT TT (CTTT)$_{16}$ (CTTC)$_3$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 12(TTTC)$_4$ TTTT TT (CTTT)$_{17}$ (CTTC)$_3$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 13(TTTC)$_4$ TTTT TT (CTTT)$_8$ (CTGT)$_4$ (CTTT)$_{13}$ (CTTC)$_4$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 14(TTTC)$_4$ TTTT TT (CTTT)$_8$ (CTGT)$_5$ (CTTT)$_{13}$ (CTTC)$_4$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 15(TTTC)$_4$ TTTT TT (CTTT)$_{11}$ (CTGT)$_3$ (CTTT)$_{14}$ (CTTC)$_3$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 16(TTTC)$_4$ TTTT TT (CTTT)$_{10}$ (CTCT)$_5$ (CTTT)$_{13}$ (CTTC)$_4$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 17(TTTC)$_4$ TTTT TT (CTTT)$_{12}$ (CTGT)$_5$ (CTTT)$_{14}$ (CTTC)$_3$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 18(TTTC)$_2$ TTTT TT (CTTT)$_{14}$ (CTGT)$_3$ (CTTT)$_{14}$ (CTTC)$_4$ (CTTT)$_3$ CTCC (TTCC)$_4$-; SEQ ID NO 19(TCTA)$_4$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)2 TCCATA (TCTA)$_6$ TCGTCT-; SEQ ID NO 20(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_9$ TCGTCT-; SEQ ID NO 21(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_2$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{10}$ TCGTCT-; SEQ ID NO 22(TCTA)$_4$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_8$ TCGTCT-; SEQ ID NO 23(TCTA)$_5$ (TCTG)$_5$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_9$ TCGTCT-; SEQ ID NO 24(TCTA)$_4$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{10}$ TCGTCT-; SEQ ID NO 25(TCTA)$_4$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{11}$ TCGTCT-; SEQ ID NO 26(TCTA)$_6$ (TCTG)$_5$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{11}$ TCGTCT-; SEQ ID NO 27(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{12}$ TCGTCT-; SEQ ID NO 28(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{11}$ TA TCTA TCGTCT-; SEQ ID NO 29(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{12}$ TA TCTA TCGTCT-; SEQ ID NO 30(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{13}$ TA TCTA TCGTCT-; SEQ ID NO 31(TCTA)$_5$ (TCTG)$_6$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{14}$ TATCTA TCGTCT-; SEQ ID NO 32(TCTA)$_{10}$ (TCTG)$_5$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{12}$ TCGTCT-; SEQ ID NO 33(TCTA)$_{11}$ (TCTGT)$_5$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{12}$ TCGTCT-; SEQ ID NO 34 (TCTA)$_{11}$ (TCTG)$_5$ (TCTA)$_3$ TA (TCTA)$_3$ TCA (TCTA)$_2$ TCCATA (TCTA)$_{13}$ TCGTCT; SEQ ID NO 35(TCTA)$_{13}$ (TCTG)$_5$ (TCTA)$_3$ TA

$(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT;and SEQ. ID NO: 36$(AGAA)_8$-. wherein the isolated single-stranded nucleic acid is covalently labeled with a dye.

Amendment type: Label

Notes: The *Myriad*-based rejection was initially raised in a non-final rejection (11 September 2013). The addition of the highlighted text was made in response to that rejection, albeit without the term "covalently". Since the next office action (final rejection of 21 February 2014) did not reiterate the *Myriad*-based rejection, this amended appeared to transform the claim into patent eligible subject matter. A non-final office action (3 June 2014), however, raised the issue again against the amended claim. In this non-final office action, the examiner applied new guidelines on subject matter eligibility. The examiner found the label did not make the product 'markedly different' from that in nature and that the addition of a label did not "impose meaningful limit" on the claim's scope. That the label must be "covalently labelled" was an examiner's amendment, made in the notice of allowance (12 September 2014).

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17. Title: Human Immunodeficiency Virus And Uses Thereof

Application Publication No: 2011/0281258 A1
Application No: 13/028,816
Relevant Claim:

1. An isolated complete nucleic acid of the HIV-1 Group P virus wherein the nucleic acid comprises SEQ ID NO: 1.

Grant Publication No: 9150834 B2
Relevant Grant Claim:

1. An isolated nucleic acid of an HIV-1 Group P virus, wherein the nucleic acid consists of SEQ ID NO: 1 and the isolated nucleic acid is labeled with a radioactive compound or with a nonradioactive compound.

Amendment type: Label

Notes: In response to the *Myriad*-based rejection, the applicant initially tried to overcome the rejection by arguing that SEQ ID NO: 1 is isolated proviral DNA (a DNA form of the RNA-based virus that exists when integrated in a host-cell genome). Further, the applicant argued that since the purpose of integration into a cell is to ultimately replicate itself, if the DNA is isolated (as in the claim) then the DNA no longer has this function (see applicant arguments, 24 July 2014). The examiner rejected this argument because the HIV genome is transcribed/reverse transcribed as "both RNA and DNA so it does not appear that amending to a specific nucleic acid will remove the rejection."

Type 5: Vector

18. Title: Method For Predicting And Detecting Tumor Metastasis

Application Publication No: 2011/0152355 A1
Application No: 13/006,603
Relevant Claim:

37. An isolated nucleic acid consisting of a nucleic acid sequence that only encodes the amino acid sequence of SEQ ID NO: 2.

    (The claims in this application were amended many times during prosecution. This claim first appeared in this form 9 October 2012. This is the first-listed isolated-nucleotide claim that received a *Myriad*-based rejection).

Grant Publication No: 8816059 B2
Relevant Grant Claim:

2. A vector comprising a nucleic acid consisting of a nucleic acid sequence that only encodes the amino acid sequence of SEQ ID NO: 2.

Amendment type: Vector

Notes: Claims to cDNA for the same sequence were also made. These cDNA claims, however, were added part way through prosecution.

Type 6: Recombination with non-specific regulatory nucleic acid

19. Title: Polynucleotides Encoding Proteins Involved In Plant Metabolism

Application Publication No: 2013/0007912 A1
Application No:
Relevant Claim:

1. An isolated polynucleotide comprising:
(a) a nucleotide sequence encoding a polypeptide, wherein the amino acid sequence of the polypeptide has at least 90% sequence identity, based on the Clustal alignment method with pairwise alignment default parameters of KTUPLE=1, GAP PENALTY=3, WINDOW=5 and DIAGONALS SAVED=5, with SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, or 362; or
(b) a complement of the nucleotide sequence of (a), wherein the complement and the nucleotide sequence consist of the same number of nucleotides and are 100% complementary.

Grant Publication No: 8658858 B2
Relevant Grant Claim:

1. A recombinant DNA construct comprising:
(a) a nucleotide sequence encoding a phosphatidylinositol transfer polypeptide, wherein the amino acid sequence of the polypeptide has at least 90% sequence identity, based on the Clustal alignment method with pairwise alignment default parameters of KTUPLE=1, GAP PENALTY=3, WINDOW=5 and DIAGONALS SAVED=5, with SEQ ID NO:320; or
(b) a complement of the nucleotide sequence of (a), wherein the complement and the nucleotide sequence consist of the same number of nucleotides and are 100% complementary, and wherein the nucleotide sequence is operably linked to at least one regulatory sequence.

Amendment type: Non-specific recombination

Notes: The *Myriad*-based rejection was raised in an examiner-initiated interview (8 August 2013), when the applicant also authorised the examiner-suggested amendment.

Type 7: Nucleic acid with non-naturally occurring sequence variations and a negative-claim clause

20. Title: Methods And Nucleic Acids For Analyses Of Cellular Proliferative Disorders

Application Publication No: 2011/0244458 A1
Application No: 13/096,932
Relevant Claim:

2. A treated nucleic acid derived from genomic SEQ ID NOS:1 to SEQ ID NO:3, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NOS:159 to SEQ ID NO:167, wherein the treatment is suitable to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine in terms of hybridization.

Grant Publication No: 8900829 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs: 30, 31, 42, and 43, wherein the nucleic acid molecule is not identical or complementary to all or a portion of SEQ ID NO: 24 or other naturally occurring DNA.

Amendment type: Modification with negative claim

Notes: The applicant supported this amendment by pointing out that SEQ ID NOs: 30, 31, 42 and 43 were created through bisulfite treatment of genomic DNA consisting of SEQ ID NO 24. Bisulfite treatment converts unmethylated cytosines to uracil, creating nucleic acid molecules that do not exist in nature (see applicant arguments, 18 April 2014).

Type 8: Short nucleotide

21. Title: Spanx-b Polypeptides And Their Use

Application Publication No: 2011/0318374 A1 (note: this link does not contain a pdf of the application, instead, see Google patents: 2011/0318374 A1).
Application No: 13/203,042
Relevant Claim:

> 17. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 13.
>
> (Claim 13: An isolated polypeptide comprising: the amino acid sequence set forth as
> (a) SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 26, SEQ ID NO: 27, or SEQ ID NO: 28; or
> (b) at least nine consecutive amino acids of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 5;
> wherein the polypeptide is nine to twelve amino acids in length.)

Grant Publication No: 8664183 B2
Relevant Grant Claim:

> 8. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 6.
>
> (Claim 6: An isolated polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 2, wherein the polypeptide is nine to twelve amino acids in length.)

Type: Short nucleic acid

Notes: During an applicant-initiated interview the parties discussed the applicability of *Myriad* to application claim 17 (10 July 2013). The examiner indicated that the claim would not receive a *Myriad*-based objection because "the polynucleotides would not naturally encode a 9-12-mer as recited in [application] claim 13."

Application claim 13 was amended during prosecution due to a restriction requirement (see applicant arguments (30 October 2012) and requirement for restriction/election (1 October 2012).

Cancelled

22. Title: Tumor Antigens Bfa4 And Bcy1 For Prevention And / Or Treatment Of Cancer

Application Publication No: US2011/0117640A1 A1
Application No: 12/888,975
Relevant Claim:

1. An isolated nucleic acid molecule comprising SEQ ID NO.: 3.

Grant Publication No: 8946174 B2
Relevant Grant Claim: N/A

Amendment type: Cancelled.

Notes: The granted patent claims vectors in various forms, including a claim to a 'vector comprising the nucleic acid consisting of SEQ ID NO.:3.' It also claims pharmaceutical compositions with a vector as part of the composition.

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23. Title: Method For The Detection And Diagnosis Of Cancer Involving Primers And Probes For The Specific Detection Of The Mage-a3-marker

Application Publication No: 2012/0040341 A1
Application No: 12/305,742
Relevant Claim:

1. A set of primers consisting of the pair of primers SEQ ID NO:11 and SEQ ID NO:12.

Grant Publication No: 8936919 B2
Relevant Grant Claim: N/A

Amendment type: Cancelled.

Note: Initially the applicant attempted to overcome the *Myriad*-based objection by arguing that the claim was to a *particular set of two* isolated nucleic acid molecules (applicant arguments, 7 May 2014). The examiner rejected this argument because primers, even as a set, are not structurally different from their natural counterparts (final rejection, 6 August 2014).

Although this claim was cancelled, the granted patent included claims to probes (with fluorescent dye), methods of diagnoses and kits (with primers and probes) were granted.

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24. Title: Nucleic Acids Encoding Biologically Active Polypeptides Derived From A Novel Early Stage Pregnancy Factor Designated Maternin (ma)

Application Publication No: 2012/0083587 A1
Application No: 13/159,285
Relevant Claim:

1. An isolated nucleic acid encoding a therapeutic polypeptide selected from the group consisting of:
   (a) a polypeptide selected from the group consisting of:

(SEQ ID NO: 2)(i)MA peptide; (SEQ ID NO: 3)(ii)pMA peptide;
(b) a polypeptide comprising one or more amino acid sequences selected from the group consisting of:
(i) the amino acid sequence of MA (SEQ ID NO: 2);
(ii) the amino acid sequence of pMA (SEQ ID NO: 3);
(iii) the amino acid sequence of MA_{S1} (SEQ ID NO: 4);
(iv) the amino acid sequence of MA_{S2} (SEQ ID NO: 5);
(v) the amino acid sequence of MA_{S3} (SEQ ID NO: 6);
(vi) the amino acid sequence of MA_{S5} (SEQ ID NO: 7);
(vii) the amino acid sequence of MA_{S9} (SEQ ID NO: 8);
(viii) the amino acid sequence of MA_{S10} (SEQ ID NO: 9);
(ix) the amino acid sequence of MA_{S11} (SEQ ID NO: 10);
(x) the amino acid sequence of β-hCG 55-88 (SEQ ID NO: 11);
(xi) the amino acid sequence of β-hCG 55-90 (SEQ ID NO: 12);
(xii) the amino acid sequence of β-hCG 55-91 (SEQ ID NO: 13);
(xiii) the amino acid sequence of β-hCG 55-74 (SEQ ID NO: 14);
(xiv) the amino acid sequence of β-hCG 6-37 (SEQ ID NO: 15);
(xv) the amino acid sequence of β-hCG 6-38 (SEQ ID NO: 16);
(xvi) the amino acid sequence of β-hCG 6-39 (SEQ ID NO: 17);
(xvii) the amino acid sequence of β-hCG 6-40 (SEQ ID NO: 18); and
(c) functional equivalents of the polypeptides of 1(a) and (b);
With the proviso that 1(b), and 1(c) exclude the full length sequence of (SEQ ID NO: 1).

Grant Publication No: 9175077 B2
Relevant Grant Claim: N/A

Amendment type: Cancelled.

Notes: The non-final rejection that included the *Myriad*-based rejection (19 December 2013) was made *after* a notice of allowance (13 June 2013) had been issued.

The applicant attempted to overcome the rejection by amending the claim to state the isolated nucleic acid is "operationally linked to a promoter" (applicant arguments, 18 June 2014); this amendment was modelled on an examiner-suggested amendment, "operably linked to a heterologous promoter" (non-final rejection, 19 December 2013). The applicant's amendment, however, was rejected because it is "well-known that various promoters and enhancers are present in the human genome and facilitate the expression of various gene products" (final rejection, 9 October 2014). The examiner reiterated that if the nucleic acid were linked to a *heterologous* promoter that this would be patent eligible (final rejection, 9 October 2014). The applicant did not adopt this amendment, instead, cancelling the claim.

Although this claim was cancelled, the granted patent claimed a vector including a nucleic acid sequence that that encoded a polypeptide of SEQ ID No 2. Claims were also granted to cells comprising this vector.