

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00016

U.S. Patent No. 10,876,108 B2

PETITIONER'S DEMONSTRATIVE EXHIBITS

**United States Patent and Trademark Office
Before the Patent Trial and Appeal Board**

***Integrated DNA Technologies, Inc.
v. Tecan Genomics, Inc.***

Petition for Inter Partes Review
Case Nos. IPR2025-00015 and IPR2025-00016
U.S. Patent Nos. 10,036,012 and 10,876,108*

Petitioner's Demonstratives

Oral Hearing: January 22, 2026

Sole Dispute On Most Claims Is “Enrichment” Limitations

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Sole Dispute On Most Claims Is “Enrichment” Limitations

'012 Patent, Claim 1	'108 Patent, Claim 1	
A method for sequencing an enriched nucleic acid sequence of interest , the method comprising:		
1(a) ligation		✓
1(b) annealing	1(a) annealing	✓
1(c) extending	1(b) extending	✓
1(d) amplifying	1(c) amplifying	
1(e) surface annealing		✓
1(f) sequencing	1(d) sequencing	

Sole Dispute On Most Claims Is “Enrichment” Limitations

'012 Patent, Claim 1	'108 Patent, Claim 1	
"d)amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest,"	method	
		✓
		✓
	1(b) extending	✓
1(d) amplifying	1(c) amplifying	
1(e) surface annealing		✓
1(f) sequencing	1(d) sequencing	

Sole Dispute On Most Claims Is “Enrichment” Limitations

'012 Patent, Claim 1	'108 Patent, Claim 1	
A method for sequencing an enriched nucleic acid sequence of interest , the method comprising:		
1(a) ligation		✓
1(b) annealing	1(a) annealing	✓
"f) Sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform"		✓
1(e) surface annealing		✓
1(f) sequencing	1(d) sequencing	

Sole Dispute On Most Claims Is “Enrichment” Limitations

'012 Patent, Claim 1		
A method for sequencing enriched nucleic acid sequences comprising:	"c) amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest"	
1(a) ligation		
1(b) annealing		
1(c) extending		
1(d) amplifying		
1(e) surface annealing	1(b) extending	✓
1(f) sequencing	1(c) amplifying	✓

Sole Dispute On Most Claims Is “Enrichment” Limitations

'012 Patent, Claim 1	'108 Patent, Claim 1	
A method for sequencing an enriched nucleic acid sequence of interest , the method comprising:		
1(a) ligation		✓
1(b) annealing	1(a) annealing	✓
1(c) extending	"d) Sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform"	
1(d) amplifying		
1(e) surface annealing		✓
1(f) sequencing	1(d) sequencing	

Claim Construction of "Enrich"

Tecan's "Claim Construction" Is a Moving Target

Claim Term

Claim 1(d)

“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to **enrich for** the nucleic acid sequence of interest”

'012 Patent, Claim 1(d)

Tecan's "Claim Construction" Is a Moving Target

Claim Term

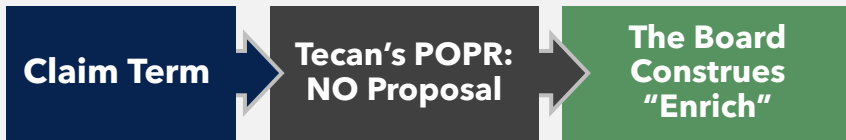
Tecan's POPR:
NO Proposal

Claim 1(d)

“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to **enrich for** the nucleic acid sequence of interest”

'012 Patent, Claim 1(d)

Tecan's "Claim Construction" Is a Moving Target



Claim 1(d)	The Board's Construction
“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3’ end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest” '012 Patent, Claim 1(d)	“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3’ end to a complement of the second adaptor sequence to add or increase the proportion of the nucleic acid sequence of interest”

Tecan's "Claim Construction" Is a Moving Target

Claim Term

Tecan's POPR:
NO Proposal

The Board
Construes
"Enrich"

Decision Granting IPR

"Neither party proposes any special meaning for the term 'enrich.' We see no reason to do so either. To the extent express construction of 'enrich' is necessary, we adopt the plain and ordinary meaning of the term. See Ex. 3001 (entry e defining 'enrich' to mean 'to process so as to add or increase the proportion of a desirable ingredient')."

'012 Patent, Claim 1(d)

Tecan's "Claim Construction" Is a Moving Target



Claim 1(d)	The Board's Construction
"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest" '012 Patent, Claim 1(d)	"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to add or increase the proportion of the nucleic acid sequence of interest" The Meyer method adds or increases the proportion of 3' end fragments

Tecan's "Claim Construction" Is a Moving Target



Claim 1(d)	The Board's Construction 	Tecan's POR Proposed Construction
"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest" '012 Patent, Claim 1(d)	"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to add or increase the proportion of the nucleic acid sequence of interest" The Meyer method adds or increases the proportion of 3' end fragments	"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to ~~add or~~ increase the proportion of the nucleic acid sequence of interest <u>relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement</u>" Tecan's expert estimates Meyer increases the proportion of 3' end fragments

Tecan's "Claim Construction" Is a Moving Target



Tecan POR

“In the context of preparing a sequencing library, Tecan proposes that a nucleic acid sequence of interest is ‘enriched’ when the proportion of nucleic acid fragments containing the sequence of interest is increased relative to other nucleic acid fragments in the sample.”

'012 Patent, Claim 1(d)

The Meyer method adds or increases the proportion of 3' end fragments

relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement”

Tecan's expert estimates Meyer increases the proportion of 3' end fragments

Tecan's "Claim Construction" Is a Moving Target



Claim 1(d)	The Board's Construction ✓	Tecan's POR Proposed Construction ✓	Tecan's Sur-Reply Brief
"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest" '012 Patent, Claim 1(d)	"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to add or increase the proportion of the nucleic acid sequence of interest" The Meyer method adds or increases the proportion of 3' end fragments	"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to ~~add or~~ increase the proportion of the nucleic acid sequence of interest relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement" Tecan's expert estimates Meyer increases the proportion of 3' end fragments	"amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to ~~add or~~ increase the proportion of the nucleic acid sequence of interest relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement wherein only the oligonucleotide extension products from step (c) undergo the claimed amplification"

Tecan's "Claim Construction" Is a Moving Target



Claim 1(d)	The Board's Construction ✓	Tecan's POR Proposed Construction ✓	Tecan's Sur-Reply Brief
“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3’ end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest” '012 Patent, Claim 1(d)	“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3’ end to a complement of the second adaptor sequence to add or increase the proportion of the nucleic acid sequence of interest” The Meyer method adds or increases the proportion of 3’ end fragments	“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3’ end to a complement of the second adaptor sequence to ~~add or~~ increase the proportion of the nucleic acid sequence of interest <u>relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement</u>” Tecan’s expert estimates Meyer increases the proportion of 3’ end fragments	“amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3’ end to a complement of the second adaptor sequence to ~~add or~~ increase the proportion of the nucleic acid sequence of interest <u>relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement</u> ~~where only the oligonucleotide extension product from step (c) undergo the claimed amplification~~”

**“Enrich” Should Be
Given Its Plain and
Ordinary Meaning**

The Claim Language

The Claim Specifies the Steps That Constitute Enrichment

ENRICHING

'012 Patent Claim 1

“1. A method for sequencing an **enriched** nucleic acid sequence of interest, the method comprising”:

- a) **ligating**,
- b) **annealing**,
- c) **extending**,
- d) “**amplifying** the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface”;
- e) annealing to **surface**
- f) **sequencing** the enriched nucleic acid sequence of interest on NGS

'108 Patent Claim 1

“1. A method for sequencing an **enriched** nucleic acid sequence of interest, the method comprising”:

- a) **annealing**,
- b) **extending**,
- c) “**amplifying** the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest”;
- d) **sequencing** amplified products comprising the nucleic acid sequence of interest on NGS

Such a Clause Cannot Import Unrecited Limitations

Texas Instruments, Inc. v. ITC, 988 F.2d 1165, 1172 (Fed. Cir. 1993)

Clauses that “**merely describe the result of arranging the components of the claims in the manner recited in the claims . . . do not contain any limitations not inherent to the process found in [the] claims.**”

Minton v. Nat’l Ass’n of Secs. Dealers, 336 F.3d 1373, 1381 (Fed. Cir. 2003)

“A whereby clause in a method claim is not given weight when it simply **expresses the intended result of a process step positively recited.**”

Tecan Does Not Distinguish Petitioner's Cases

Tecan's Sur-Reply

“Arguing that the claims do not require enrichment, Petitioner relies exclusively on a subset of cases concerning the construction of ‘whereby’ clauses.”

Petitioner's Cases Are Not Limited to "Whereby" Clauses

<i>Tex. Instr. Claim</i>	<i>'012 Patent, Claim 1(d)</i>	<i>Minton Claim</i>	<i>'108 Patent, Claim 1(c)</i>
“fluid insulating material being injected into a portion of the cavity on the opposite side of said plane <u>to preclude</u> direct high velocity engagement between the fluid and the device and the electrical connections thereto”	“amplifying [extension products containing the sequence of interest in a specific way] <u>to enrich</u> for the nucleic acid sequence of interest”	“executing a trade of the security based on information contained in the offer for consideration specified in the reply to the offer <u>whereby</u> the security is traded efficiently between the first individual [who entered the offer] and the second individual [who entered the reply in response to the offer]”	“amplifying [extension products containing the sequence of interest in a specific way] <u>thereby enriching</u> the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest”

Tecan's Only Cited Case Is Inapposite

Tecan's Sur-Reply

“However, as is the case here, the Federal Circuit has repeatedly held that ‘when a ‘whereby’ or [similar] clause states a condition that is **material to patentability**, it cannot be ignored in order to change the substance of the invention.’ *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019) (cleaned up).”

The “wherein” Clauses in *Allergan* Stated Express Limitations

Allergan Sales, LLC v. Sandoz, Inc., 935 F.3d 1370, 1372-1373 (Fed. Cir. 2019)

“A method of treating a patient with glaucoma or ocular hypertension comprising topically administering twice daily to an affected eye a single composition comprising 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate,

wherein the method is as effective as the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day and

wherein the method reduces the incidence of one o[r] more adverse events selected from the group consisting of conjunctival hyperemia, oral dryness, eye pruritus, allergic conjunctivitis, foreign body sensation, conjunctival folliculosis, and somnolence when compared to the administration of 0.2% w/v brimonidine tartrate monotherapy three times daily.”

The “wherein” Clauses in *Allergan* Were Material to Patentability

Tecan’s Sur-Reply

“However, as is the case here, the Federal Circuit has repeatedly held that ‘when a ‘whereby’ or [similar] clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.’ *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019) (cleaned up).”

Allergan Sales, LLC v. Sandoz, Inc., 935 F.3d 1370, 1376 (Fed. Cir. 2019)

“the Examiner explicitly relied on the ‘wherein’ clauses in explaining why the claims of the Patent-in-Suit were ‘novel and non-obvious over the prior art’”

The "to enrich" Clause Was Included in the Originally Filed Claims

1. A method for enriching for target nucleic acid sequences of interest in a sample comprising nucleic acids, the method comprising:
 - a. fragmenting the nucleic acids, thereby generating nucleic acid fragments;
 - b. appending a first adaptor to a 5' end of each nucleic acid fragment;
 - c. annealing one or more oligonucleotides to the nucleic acid fragments, whereby each of the one or more oligonucleotides comprise a 3' portion that is complementary to a target nucleic acid sequence of interest present in one or more of the nucleic acid fragments, and a 5' portion comprising a second adapter sequence;
 - d. extending the one or more oligonucleotides with a polymerase thereby generating one or more oligonucleotide extension products with the first adaptor at a first end and the second adaptor sequence at a second end; and
 - e. amplifying the one or more oligonucleotide extension product using a first primer that is complementary to the first adaptor and a second primer that is complementary to the second adaptor sequence to enrich for nucleic acid fragments containing the first adaptor and the second adaptor sequence at each end.

The "to enrich" Clause Was Not Material to Patentability

Jones 2005 disclosed every step of the claimed method except sequencing on a Next Generation Sequencer

Regarding claims 51, 63-67, 69, and 75, Jones teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids that comprises the following steps (see, for example, Figures 3-4 and paragraphs 86-90, 96, 99, and 100): (a) fragmenting nucleic acids in the sample to generate fragments comprising the sequence of interest; (b) ligating a partial duplex adaptor to each 5' and each 3' end of the nucleic acid fragments, wherein the partial duplex adaptor comprises a first long strand containing a first adaptor sequence and second shorter strand; (c) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the fragments, wherein said oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence; (d) extending said annealed oligonucleotides using a DNA polymerase, thereby obtaining extension products comprising sequence complementary to

Jones **does not teach massively parallel sequencing** as required by independent claim 51.

sequence to enrich for the nucleic acid sequence of interest; and (f) sequencing the enriched nucleic acid of interest.

None of Tecan's Arguments Support Adding Limitations Beyond the Plain and Ordinary Meaning of "Enrich"

Tecan's Sur-Reply

“Enrichment of the target sequence resulting from the amplification step is critical to the invention. This language in step 1(d) is the antecedent basis for ‘the enriched nucleic acid sequence of interest’ in step 1(f), which Petitioner’s construction improperly ignores.”

Petitioner and Dr. Sims Do Not Dispute That Amplification Is Critical to Enrichment



Dr. Peter Sims
Expert for IDT

"I agree that ***amplification in step 1D is part of the enrichment process.***"

"Amplification is a key step in the enrichment process.
I just don't want to claim that it's the only thing going on here."

"This is a method for sequencing an enriched nucleic acid sequence of interest. It's a multistep process, and I don't want to attribute causality that isn't clearly stated in the claim to any one step. ***They're all important steps that are contributing to enrichment of a nucleic acid sequence of interest.***"

Tecan's Expert Confirmed the POSA Would Agree With the Board's Plain and Ordinary Meaning Construction



**Dr. Carlos
Bustamante**
Expert for Tecan

149. The Board construed “enrich” to have its plain and ordinary meaning of “to process so as to add or increase the proportion of a desirable ingredient.” *Id.*

I agree that a POSA would have considered the term “enrich” to have its plain and ordinary meaning and that the Panel’s definition reflects that meaning.

The Intrinsic Record

The Intrinsic Record Does Not Limit “Enrich”

- ✗ No definition**
- ✗ No lexicography or disclaimer**
- ✗ No explanation or instruction for how to quantify enrichment**
- ✗ No minimum amount of enrichment required**

No Definition, Lexicography, or Disclaimer

'012 Patent

adaptor sequence at a second end; and (e) amplifying the one or more oligonucleotide extension product using a first primer that is complementary to the first adaptor and a second primer that is complementary to the second adaptor sequence to enrich for nucleic acid fragments containing the first adaptor and the second adaptor sequence at each end. In

sequence at the second end; and (d) amplifying the one or more oligonucleotide extension products using a first primer that is complementary to the first adaptor and a second primer that is complementary to the third adaptor sequence to enrich for nucleic acid fragments containing the first adaptor and the third adaptor sequence at each end. In one

and the second end comprises the 3' end. The one or more oligonucleotide extension products can be amplified using a first primer that can be complementary to the first or second adaptor and a second primer that can be complementary to the third adaptor sequence to enrich for nucleic acid fragments comprising the first or second adaptor and the third adaptor sequence at each end. In one embodiment, the first

'108 Patent

of the first adaptor at the second end; and (h) amplifying the one or more single stranded nucleic acid fragments comprising the one or more target nucleic acid sequences with a first primer comprising sequence complementary to the strand from the second adapter and a second primer comprising sequence complementary to the short strand of the first adaptor, thereby enriching for the one or more target nucleic acid sequences. In one embodiment, the method

No Minimum Amount of Enrichment Required



Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

"Q. If I do a multiplex PCR reaction with different primer pairs, and I get more fragments from one set of primer pairs than another, have I enriched for that fragment?

A. I think ***any PCR could be described as enrichment*** if you wanted to use it in that way because you've amplified a product, you've amplified a target, such that it - it's more - its relative frequently [sic] is higher in the product than it was in the initial template."

"Q. ***If I create one more copy of the sequence*** than would otherwise be there, have I ***enriched*** for that sequence?

A. It seems that ***you could argue that if you had sufficient evidence that you truly had increased it by one copy number . . .***"

No Minimum Amount of Enrichment Required



Dr. Carlos
Bustamante
Expert for Tecan

"Q. Is there a threshold amount by which the fragment has to be enriched at the end?

A. There is **no threshold specifically laid out in the patent.**"

Tecan's Unrecited Limitation

Tecan's New Limitation Is Not in Its Construction

Tecan's Sur-Reply Brief

~~Tecan POR~~

“In the context of preparing a sequencing library, Tecan proposes that a nucleic acid sequence of interest is ‘enriched’ when the proportion of nucleic acid fragments containing the sequence of interest is increased relative to other nucleic acid fragments in the sample.”

“wherein only the oligonucleotide extension products from step (c) undergo the claimed amplification”

None of Tecan's Proposed Language Appears in the Claim

'012 Patent Claim 1

“1. A method for sequencing an **enriched** nucleic acid sequence of interest, the method comprising”:

- a) **ligating**,
- b) **annealing**,
- c) **extending**,
- d) “**amplifying** the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence **to enrich** for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface”;
- e) annealing to **surface**
- f) **sequencing** the enriched nucleic acid sequence of interest on NGS

'108 Patent Claim 1

“1. A method for sequencing an **enriched** nucleic acid sequence of interest, the method comprising”:

- a) **annealing**,
- b) **extending**,
- c) “**amplifying** the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, **thereby enriching** the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest”;
- d) **sequencing** amplified products comprising the nucleic acid sequence of interest on NGS

Tecan Seeks to Import a Negative Limitation

Tecan's Sur-Reply

“Petitioner incorrectly alleges that Tecan seeks to import the limitation that ‘only the oligonucleotide extension products from step (c) undergo the claimed amplification’ from Figure 1. Paper 47, 10-11. As Tecan has explained, the claimed inventions enrich a target sequence through amplification because of the claimed combination of a target-specific primer and a set of universal primers. Paper 41, 14-16. This is not an added limitation but simply how the invention functions. There is no need for the Board to decide whether other amplification can occur in addition to the enrichment step because Petitioner only cites prior art where all fragments undergo amplification, which does not meet limitation 1(d).”

“Simply how the invention functions” Is Not a Basis for Importing an Unrecited Limitation

Tecan’s Sur-Reply

“This is not an added limitation but simply how the invention functions.”

“Simply how the invention functions” Is Not a Basis for Importing an Unrecited Limitation

Tecan’s Sur-Reply

“This is not an added limitation but simply how the invention functions.”

Purdue Pharma v. Endo Pharm., 438 F.3d 1123, 1135 (Fed. Cir. 2006)

The trial court construed the claims to require acceptable pain control for 90% of patients over a four-fold dosage range. **Despite the absence of an express claim limitation to that effect**, the trial court held that **the “invention itself,”** *i.e.*, the “controlled release oxycodone formulation,” **was limited** to a four-fold dosage range that controls pain for 90% of patients.

“Simply how the invention functions” Is Not a Basis for Importing an Unrecited Limitation

Tecan’s Sur-Reply

“This is not an added limitation but simply how the invention functions.”

Purdue Pharma v. Endo Pharm., 438 F.3d 1123, 1136 (Fed. Cir. 2006)

The only way the trial court could hold that the four-fold dosage range was a claim limitation, then, was to state that the “invention itself” controlled pain in approximately 90% of patients with a four-fold dosage range. Without any specific claim language to interpret, however, the trial court impermissibly imported a limitation into the claims.

The Claim Recites Steps Performed on a Single Nucleic Acid Fragment

'012 Patent, Claim 1: A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:

- a) obtaining **a nucleic acid fragment** and a partial duplex adaptor,
wherein ~~the nucleic acid fragment~~ comprises a nucleic acid sequence of interest,
where **the nucleic acid fragment** is hybridized to a first adaptor sequence, and
wherein the partial duplex adaptor comprises a first strand and a second strand, wherein the first strand is longer than the second strand;
- b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest to the partial duplex adaptor, **the nucleic acid fragment**
wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and
a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;
- c) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest to the partial duplex adaptor with a polymerase, **the nucleic acid fragment**
thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
- d) amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest,
wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;
- e) annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
- f) sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

Claim 1 of the '108 Patent Confirms the Claim Does Not Limit "Other" Fragments

'108 Patent, Claim 1: A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:

a) annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in **a nucleic acid fragment**,

wherein the reaction mixture comprises a plurality of nucleic acid fragments,

wherein **the nucleic acid fragment** comprising the nucleic acid sequence of interest comprises a first adaptor sequence,

wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest

and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;

b) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in **the nucleic acid fragment** comprising the first adaptor sequence with a polymerase, in the reaction mixture,

thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;

c) amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest; and

d) sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

Tecan Cites No Disclaimer or Disavowal

Unwired Planet v. Apple, 829 F.3d 1353, 1358 (Fed. Cir. 2016)

“A disclaimer or disavowal of claim scope must be **clear and unmistakable**, requiring ‘**words or expressions of manifest exclusion or restriction**’ in the intrinsic record.”

None of Tecan's Record Cites Are Definitions or Lexicography That Limit the Plain and Ordinary Meaning of "Enrich"

Tecan's Sur-Reply

Inc., 841 Fed. App'x 210, 218 (Fed. Cir. 2021). The specification reinforces the critical nature of enrichment in the claimed invention. *See, e.g.*, EX1001.0001 ("The present invention provides methods ... for targeted nucleic acid sequence enrichment in a nucleic acid sample"), 16 (2:25-28) ("There is a need for improved methods for selective target enrichment"), 18 (6:12-16) ("methods of the invention can be used for the *selective enrichment of a plurality of defined target sequences* from complex DNA" (emphasis added)), 31 (31:41-32:42) (Example 1 determining enrichment "by calculating the number of rRNA reads as a percent of total mapped reads in the control and test samples.").

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"The present invention provides methods . . . for targeted nucleic acid sequence enrichment in a nucleic acid sample"

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“Fold enrichment is determined by calculating the number of rRNA reads as a percent of total mapped reads in the control and test samples.”

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Tecan's Negative Limitation Requires Limiting the Claim to a Preferred Embodiment

Tecan Improperly Seeks to Limit the Claim to Its Preferred Embodiment

Tecan POR

“Tecan’s Ovation and Allegro products are coextensive with the claimed methods. *Id.* The products also embody the unique SPET covered by the claimed methods.”

Tecan’s Sur-Reply

“Further, Petitioner’s attempts to minimize the importance of Figure 1’s disclosures because it depicts a ‘commercial embodiment’ (Paper 47, 10-11) are misleading. As Petitioner recognized, the patent expressly identifies Figure 1 as a ‘preferred embodiment’ of the methods described herein for enriching for target sequences of interest.’ EX1001.0023 (15:57-59).”

Tecan Exclusively Cites Descriptions of the Preferred Embodiment

Tecan POR

“The '012 patent specifies that ‘only nucleotide extension products comprising both the first and second adaptor sequence will be amplified and thus enriched.’ EX1001.0012 (12:14-17).”

be isothermal. In one embodiment, the oligonucleotide extension product comprises first adaptor sequence on one end and second adaptor sequence on the other end as generated by the methods described herein. In a preferred embodiment, the oligonucleotide extension product can be separated from the template nucleic acid fragment in order to generate a single stranded oligonucleotide extension product with first adaptor sequence on the 5' end and second adaptor sequence on the 3' end. The single stranded oligonucleotide extension product can then be amplified using a first primer comprising sequence complementary to the first adaptor and a second primer comprising sequence complementary to the second adaptor sequence. In this manner only oligonucleotide extension products comprising both the first and the second adaptor sequence will be amplified and thus enriched. In one embodiment, the first adaptor and/or the

Tecan Exclusively Cites Descriptions of the Preferred Embodiment

Tecan POR

“The specification explains repeatedly that it is this targeted amplification process of only the oligonucleotide extension products that results in enrichment of these fragments as compared to other fragments in the sample. *See id.*,.0021 (12:14-17) ([i]n this manner only oligonucleotide extension products comprising both the first and second adaptor sequence will be amplified and thus enriched’); *id.*,.0024 (17:57-60) (‘only the oligonucleotide extension product with the forward adaptor sequence at one end and the reverse adaptor sequence at the other end can be amplified and thus enriched’).”

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A schematic of a preferred embodiment of the methods described herein for enriching for target sequences of interest is illustrated in FIG. 1. Overall, FIG. 1 depicts a method

oligonucleotide with a reverse adaptor tail is directed. As illustrated in FIG. 1, a subtractive polymerase chain reaction (PCR) procedure is subsequently performed using a first primer directed against the forward adaptor sequence and a second primer directed toward the reverse adaptor sequence such that only the oligonucleotide extension product with the forward adaptor sequence at one end and the reverse adaptor sequence at the other end can be amplified and thus enriched.

Tecan Does Not Distinguish Petitioner's Case Law

Northrop Grumman v. Intel, 325 F.3d 1346, 1355 (Fed. Cir. 2003)

“The statements from the description of the preferred embodiment, moreover, are just that—descriptions of a preferred embodiment that operates [in a certain manner] . . .

Absent a clear disclaimer of particular subject matter, the fact that the inventor may have anticipated that the invention would be used in a particular way does not mean that the scope of the patent is limited to that context.”

The Patent Includes Embodiments That Differ From the Preferred Embodiment



Dr. Carlos
Bustamante
Expert for
Tecan

Example 3: Random Priming to Generate a Sequencing Library

[Discussing Example 3]

"Q. And that reference to the Ovation system means that ***this is an embodiment of the claims, right?***

A. ***Presumably that's what we would expect.***"

'012
Patent

Whole Transcriptome Sequencing

25,000 or more) of target sequences. In some cases, the plurality of target sequences may comprise a group of related sequences, random sequences, a whole transcriptome or fraction (e.g. substantial fraction) thereof, or any group of sequences such as mRNA. In some embodiments, the prim-

The Claim's Use of "Comprising" Indicates That Unrecited Steps Are Not Precluded

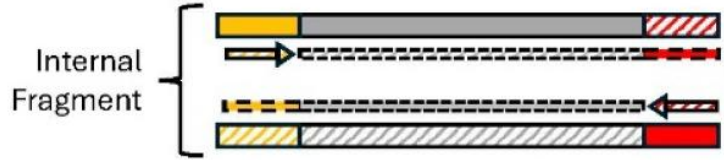
Exergen v. Wal-Mart, 575 F.3d 1312, 1319 (Fed. Cir. 2009)

Use of the term “**comprising**” “is well understood in patent law to mean “**including but not limited to**”

Invitrogen Corp. v. Biocrest Mfg, 327 F.3d 1364, 1368 (Fed. Cir. 2003)

“The transition ‘**comprising**’ in a method claim **indicates that the claim is open-ended and allows for additional steps**”

Tecan Embraces the "Comprising" Nature of the Claims for Infringement

Claimed Method	Prior Art	Alleged Infringing Products
a) ligate	Tecan argues Meyer does not satisfy the claims because internal fragments are also amplified 	The method Tecan accuses of infringement also has an unrecited amplification step 
b) anneal		
c) extend		
d) amplify		
e) anneal		
f) sequence		

Meyer Enriches Under the Board's Construction and Tecan's Original Proposed Construction

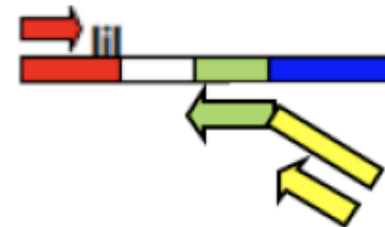
The Meyer Method “Enriched” by Using Special Chemistry to Target and Amplify 3’ End Fragments



Dr. Peter Sims
Expert for IDT

“In order to selectively enrich for sequences falling near the 3’ end of the RNA molecules, Meyer applied special chemistry to these sequences. . . . The purpose of this part of the library preparation was to selectively target and amplify—and thereby enrich—regions near the 3’ polyA tails of mRNA molecules (‘3’ end fragments,’ below), and ensure that these 3’ sequences were well-represented in the final sequencing library along with other regions of each cDNA molecule.”

3’ end fragments



The Board's Definition: The Meyer Method

"adds or increases the proportion of" 3' End Fragments

Decision Granting IPR

“Neither party proposes any special meaning for the term ‘enrich.’ We see no reason to do so either. To the extent express construction of ‘enrich’ is necessary, we adopt the plain and ordinary meaning of the term. *See* Ex. 3001 (entry defining ‘enrich’ to mean ‘to process so as to add or increase the proportion of a desirable ingredient’).”

Both of Tecan's Experts Agree the Meyer Method Exponentially "adds" to the Number of 3' End Fragments

Tecan's Expert (Dr. Bustamante)

"Q. As a result of Meyer method 1, have I increased the absolute number of 5' and 3' end fragments in the sample?

A. The absolute number?

Q. Yes.

A. You've increased the absolute number of all the molecules that undergo PCR. That's the point of PCR."

Tecan's Expert (Dr. Meyer)

"I think any PCR could be described as enrichment if you wanted to use it in that way because you've amplified a product, you've amplified a target, such that it - it's more - its relative frequency is higher in the product than it was in the initial template."

Record Shows Anticipation Under Tecan's POR Claim Construction

Tecan POR

“Tecan proposes that a nucleic acid sequence of interest is ‘enriched’ when the proportion of nucleic acid fragments containing the sequence of interest is increased relative to other nucleic acid fragments in the sample.”

Meyer Enriched Relative to Other Fragments in the Sample



Dr. Peter Sims
Expert for IDT

“The broader full-transcriptome sequencing method disclosed in Meyer is also a selective enrichment method, as it required selectively enriching for mRNA molecules over other types of RNA and other nucleic acids present in the original sample. EX1006 (Meyer) at 0020.”

Meyer Enriched Relative to Dr. Bustamante's "Baseline"



Dr. Carlos
Bustamante
Expert for Tecan

"Q. How do you define the baseline for pre-enrichment?

A. The baseline would be without practicing the claimed invention, what you would get ***without the process of targeting the nucleic acid sequence of interest, extending and then amplifying the extension product and its complement.***"

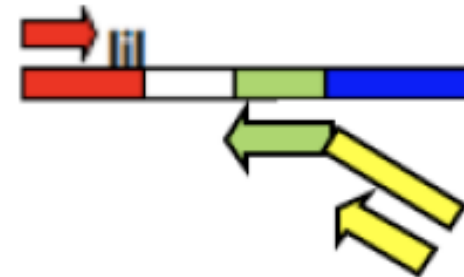
Meyer Enriched Relative to Dr. Bustamante's "Baseline"



**Dr. Carlos
Bustamante**
Expert for Tecan

“This means that once a transcript is ‘capped,’ no ligation will occur at the transcript’s termini. When Meyer later fragments the transcripts, these caps allow for the identification of the end fragments and also for Meyer to control for which adapter sequence is incorporated at the termini (more on this below).”

3' end fragments



Meyer Enriched 3' End Fragments Relative to Internal Fragments

BMC Genomics



Research article

Sequencing and de novo analysis of a coral larval transcriptome using 454 GSFx

Eli Meyer¹, Galina V Aglyamova¹, Shi Wang¹, Jade Buchanan-Carter², David Abrego³, John K Colbourne², Bette L Willis³ and Mikhail V Matz¹

Address: ¹University of Texas at Austin, 1 University Station C0930, Austin, TX, 78712, USA, ²The Center for Genomics and Bioinformatics, Indiana University, 915 East Third Street, Bloomington, IN, 47405, USA, and ³ARC Centre of Excellence for Coral Reef Studies, and School of Marine and Tropical Biology, James Cook University, Townsville, QLD, 4811, Australia

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Abstract

Background: New methods are needed for genomic-scale analysis of emerging model organisms that exemplify important biological questions but lack fully sequenced genomes. For example, there is an urgent need to understand the potential for corals to adapt to climate change, but few molecular resources are available for studying these processes in reef-building corals. To facilitate genomics studies in corals and other non-model systems, we describe methods for transcriptome sequencing using 454, as well as strategies for assembling a useful catalog of genes from the output. We have applied these methods to sequence the transcriptome of planulae larvae from the coral *Acropora millepora*.

Results: More than 600,000 reads produced in a single 454 sequencing run were assembled into ~40,000 contigs with five-fold average sequencing coverage. Based on sequence similarity with known proteins, these analyses identified ~11,000 different genes expressed in a range of conditions including thermal stress and settlement induction. Assembled sequences were annotated with gene names, conserved domains, and Gene Ontology terms. Targeted searches using these annotations identified the majority of genes associated with essential metabolic pathways and conserved signaling pathways, as well as novel candidate genes for stress-related processes. Comparisons with the genome of the anemone *Nematosella vectensis* revealed ~8,500 pairs of orthologs and ~100 candidate coral-specific genes. More than 30,000 SNPs were detected in the coral sequences, and a subset of these validated by re-sequencing.

Conclusion: The methods described here for deep sequencing of the transcriptome should be widely applicable to generate catalogs of genes and genetic markers in emerging model organisms. Our data provide the most comprehensive sequence resource currently available for reef-building corals, and include an extensive collection of potential genetic markers for association and population connectivity studies. The characterization of the larval transcriptome for this widely-studied coral will enable research into the biological processes underlying stress responses in corals and evolutionary adaptation to global climate change.

IDT Exhibit 1006.0001

Page 1 of 18
(page number not for citation purposes)

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Meyer Enriched 3' End Fragments Relative to Dr. Bustamante's Ipse Dixit



Dr. Carlos
Bustamante
Expert for Tecan

- "**Q.** What percentage would be the more appropriate one to use as the expectation, Dr. Bustamante?
- A.** I would be hard-pressed given I don't have the actual data. I just have the published distributions, but ***my sense is it is perhaps closer to 13 or 14 percent***, but again, that's a guesstimate. I have – and I think nobody has given the data that they have actually produced a reasonable way to differentiate whether the value here is demonstrating overrepresentation at all. I think it's about what they would have expected to see and that's what they claim and move on."

Tecan Wrongly Asserts Meyer's Amplification Was "Unbiased"

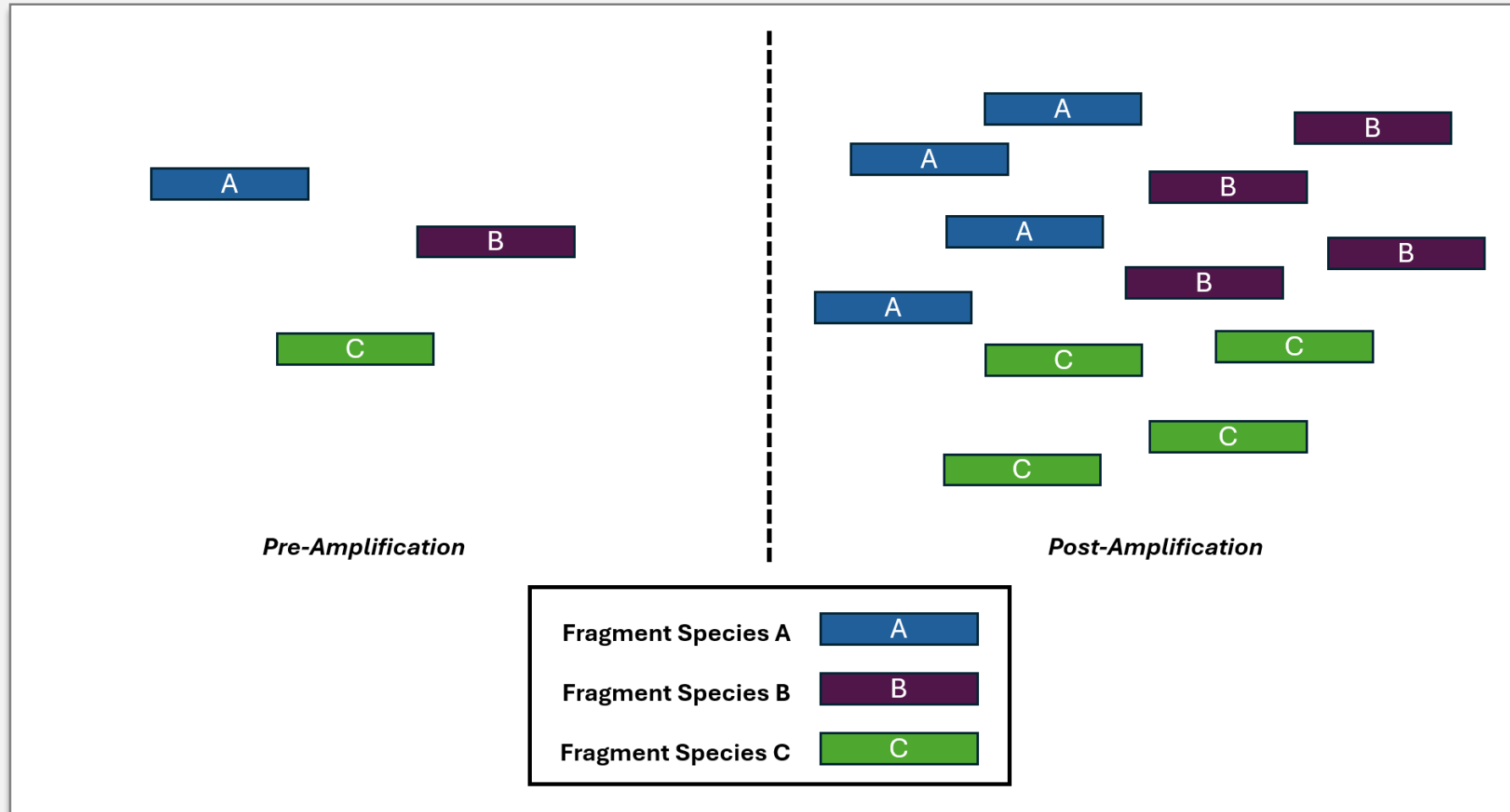
Tecan POR

"As Petitioner admits, the purpose of Meyer was to sequence the entire coral transcriptome, not to focus on any particular sequence of interest. Paper 1, 30. As such, Meyer sought to ensure that all sequences in the sample were adequately represented. Meyer does not disclose the selective amplification (i.e. enrichment) . . ."

Tecan's Sur-Reply

"*Meyer* does not disclose any enrichment since *Meyer* amplified cDNA fragments running the full length of the transcriptome in an unbiased manner. Paper 41, 27-28."

Tecan Wrongly Asserts Meyer's Amplification Was "Unbiased"



Meyer Intended to Enrich for 3' End Fragments

BMC Genomics



Research article

Open Access

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Abstract

Background: New methods are needed for genomic-scale analysis of emerging model organisms that exemplify important biological questions but lack fully sequenced genomes. For example, there is an urgent need to understand the potential for corals to adapt to climate change, but few molecular resources are available for studying these processes in reef-building corals. To facilitate genomics studies in corals and other non-model systems, we describe methods for transcriptome sequencing using 454, as well as strategies for assembling a useful catalog of genes from the output. We have applied these methods to sequence the transcriptome of planulae larvae from the coral *Acropora millepora*.

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The methods described here resolve several challenges associated with 454 sequencing of transcriptomes. Because 454 sequencing does not efficiently process homopolymer regions greater than 8 bp in length [15], the poly-A tails at the 3' ends of intact transcripts present a problem, and would be expected to result in under-representation of the 3' ends of transcripts. In our method, this is resolved by simply interrupting the poly-T region with a single C. A single copy of this 'broken-T' adaptor was found in 98,276 of the raw reads (16% of the total), slightly more than the expectation (~10%) based on average read length (232 bp) and assuming an average transcript size of 2,200 bp. This comparison suggests that the 3' ends of transcripts were well-represented in our dataset, confirming the effectiveness of this solution for overcoming the homopolymer problem. Another difficulty in 454

Meyer's Data Showed Biased Amplification

BMC Genomics



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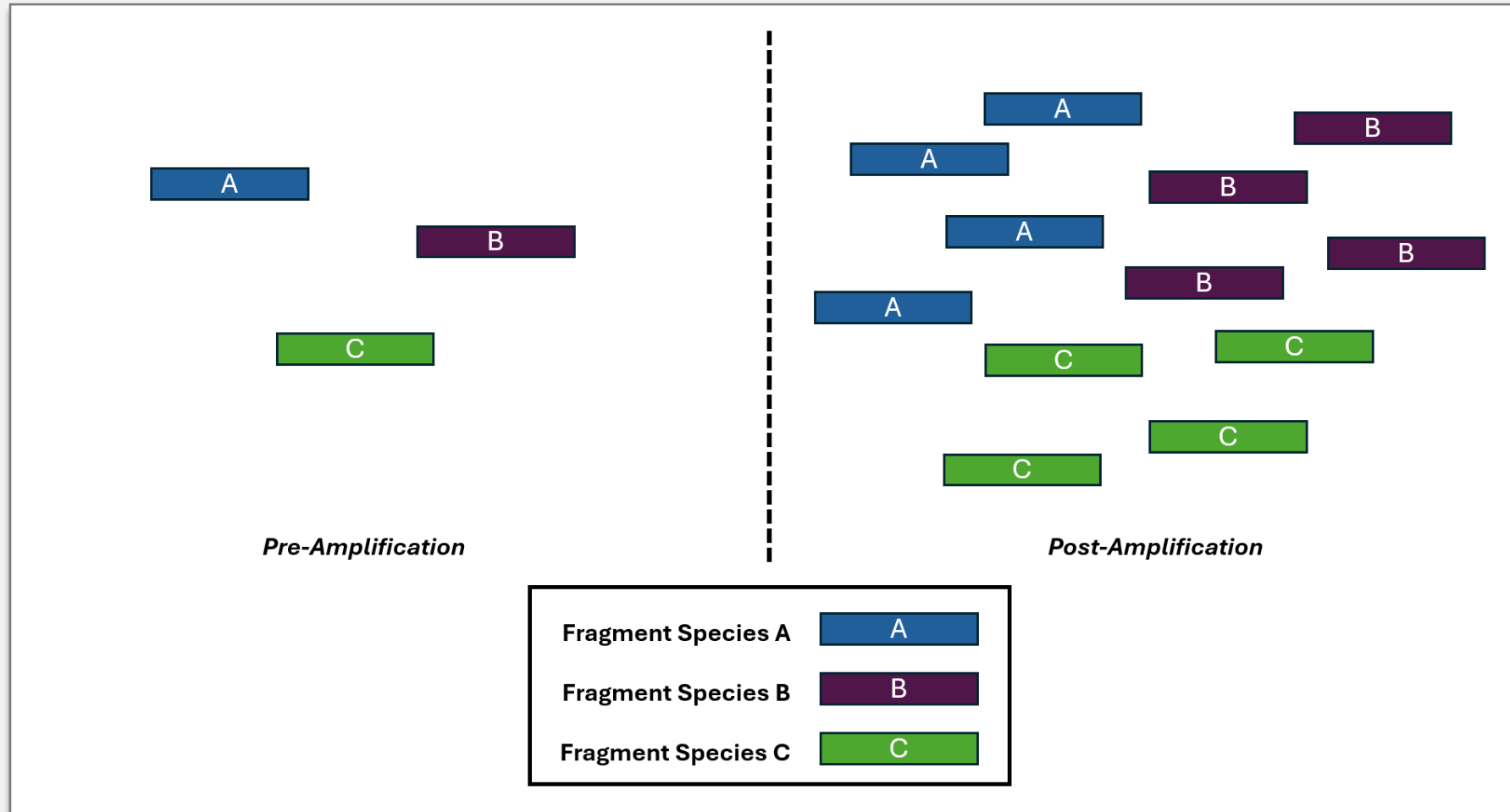
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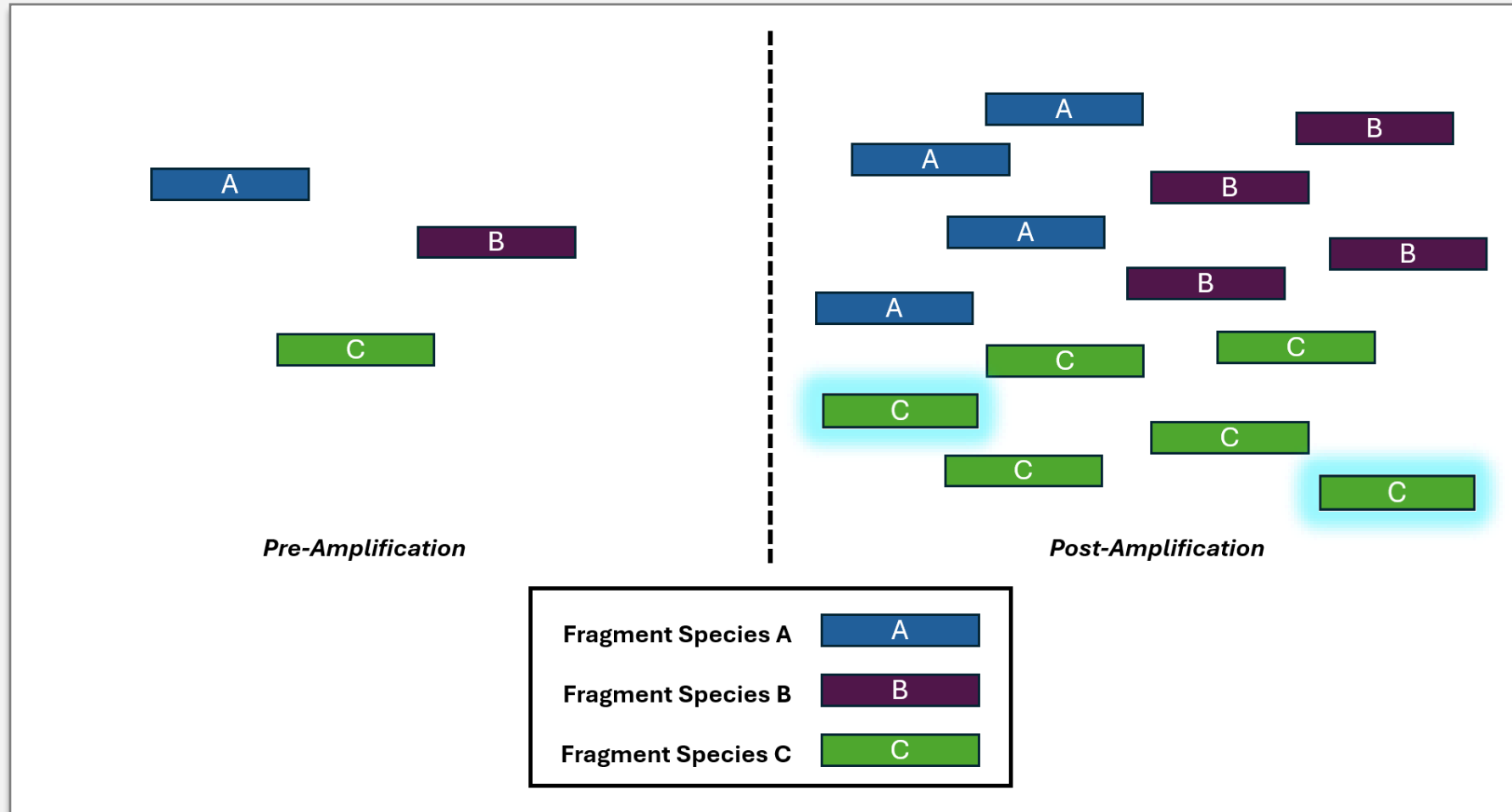
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Tecan Wrongly Asserts Meyer's Amplification Was "Unbiased"



Meyer's Data Showed Biased Amplification



"Purpose" Is Irrelevant as a Matter of Law

Homeland Housewares v. Whirlpool, 865 F.3d 1372, 1378-79 (Fed. Cir. 2017)

When all of “the structural limitations recited in [the claims] are all found in the [prior art] reference[,] . . . the absence of a disclosure relating to [intended] function does not defeat . . . [a] finding of anticipation.”

In re Schreiber, 128 F.3d 1473, 1478 (Fed. Cir. 1997)

A reference “may be directed to an entirely different problem from the one addressed by the inventor, yet the reference will still anticipate if it explicitly or inherently discloses every limitation recited in the claims.”

"Purpose" Is Irrelevant as a Matter of Law

Hewlett-Packard v. Mustek Sys., 340 F.3d 1314, 1324 n.6 (Fed. Cir. 2003)

“The anticipation analysis asks solely whether the prior art reference . . . discloses the claimed invention, and **not how the prior art characterizes that disclosure.**”

MEHL/Biophile Int'l v. Milgram, 192 F.3d 1362, 1366 (Fed. Cir. 1999)

“Nothing in the claim limits the method’s reach to human skin. Similarly, the [prior art reference]’s failure to mention hair depilation as a goal is similarly irrelevant Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that that the article’s authors did not appreciate the results.”

Tecan's Counter Arguments Fail

1

Both methods in Meyer would achieve the same result

2

The POSA would not second guess Meyer's data

Additional File 4 Is an Improved Version of the Figure 1 Method

BMC Genomics



Research article

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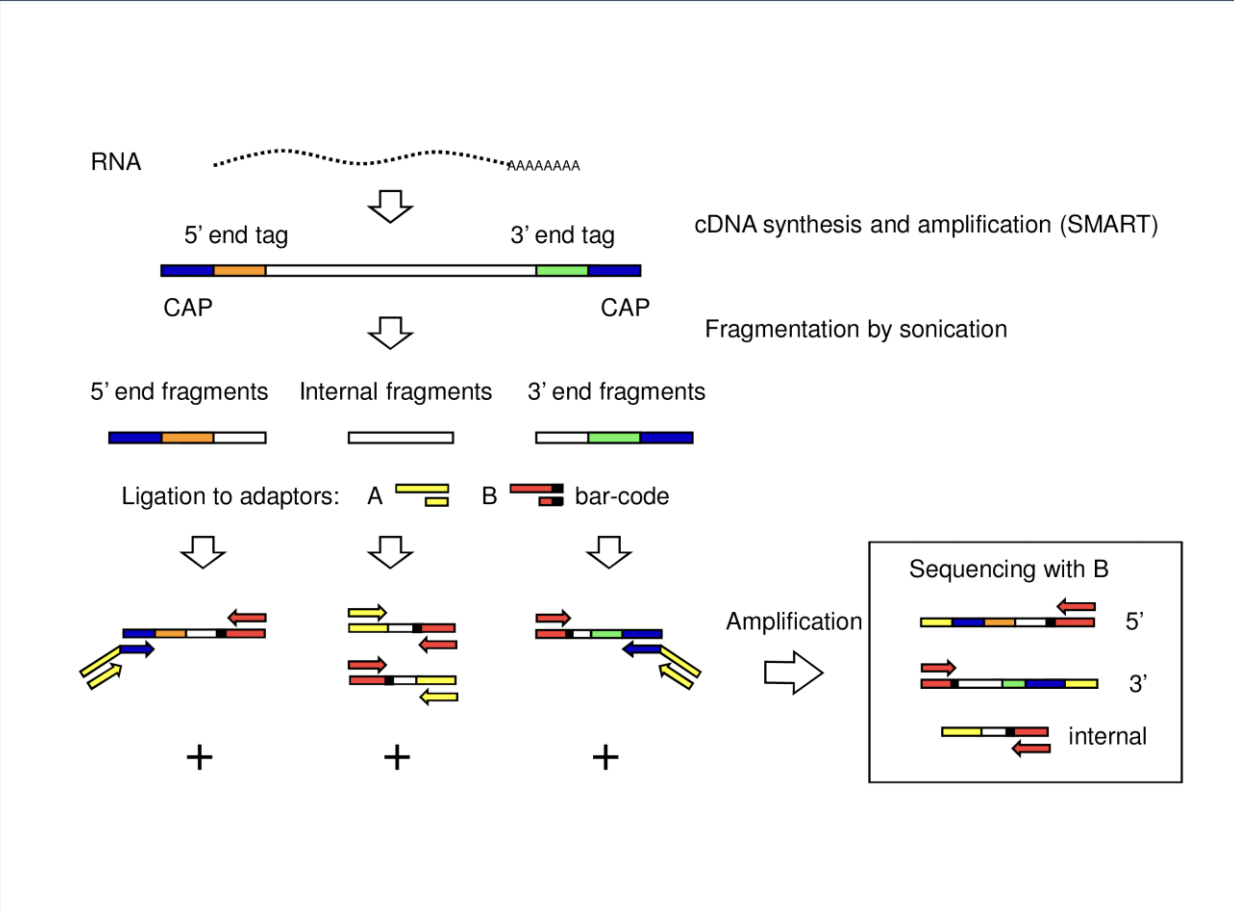
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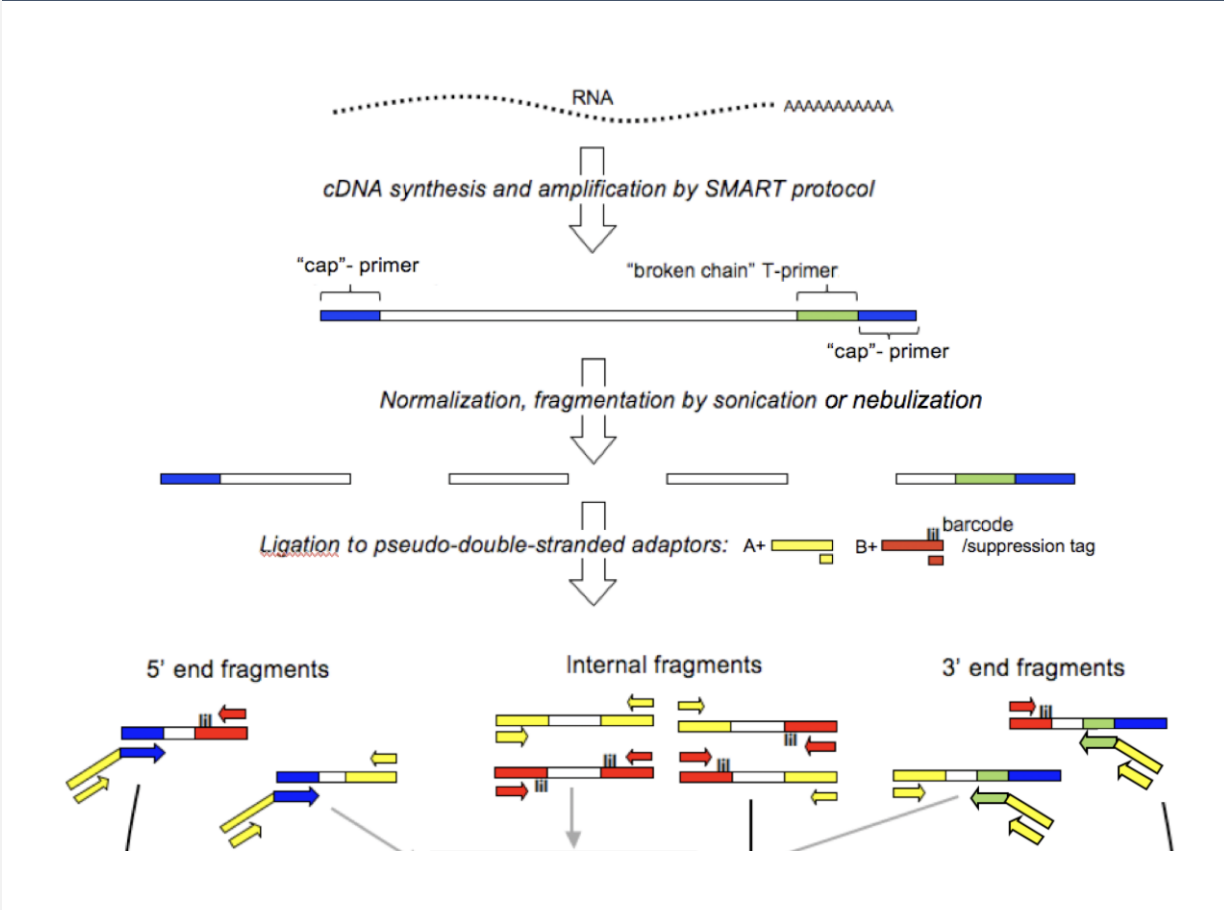
A step-by-step protocol for the library preparation method outlined above is provided in the additional files accompanying this article (additional file 4). That protocol includes minor modifications that we have recently developed to reduce the number of manipulations required, improve reproducibility, and to further reduce adaptor concatenation. The improved protocol in that file is recommended for researchers interested in using our methods for 454 sequencing of transcriptomes.

The Relevant Chemistry Is the Same in Figure 1 and Additional File 4

Figure 1

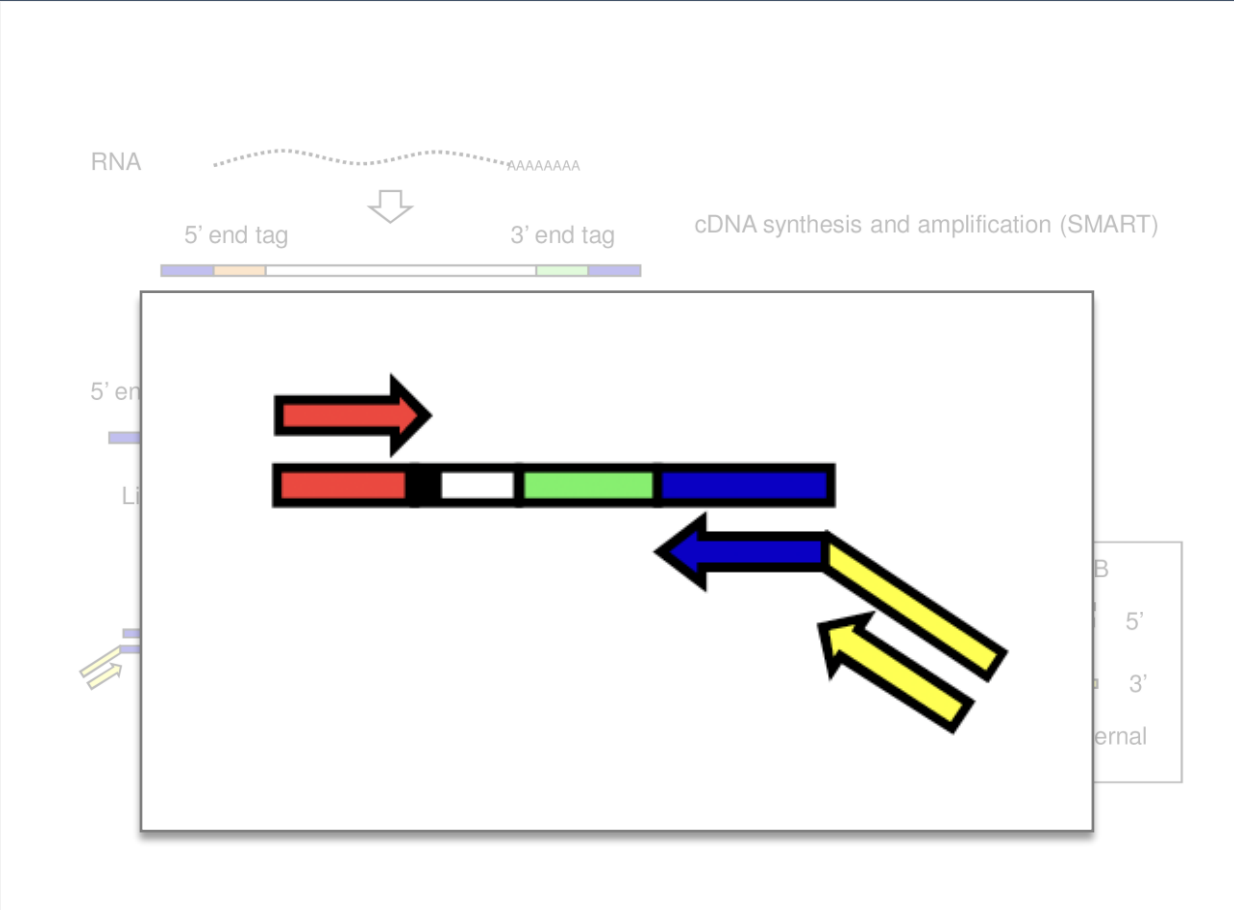


Additional File 4

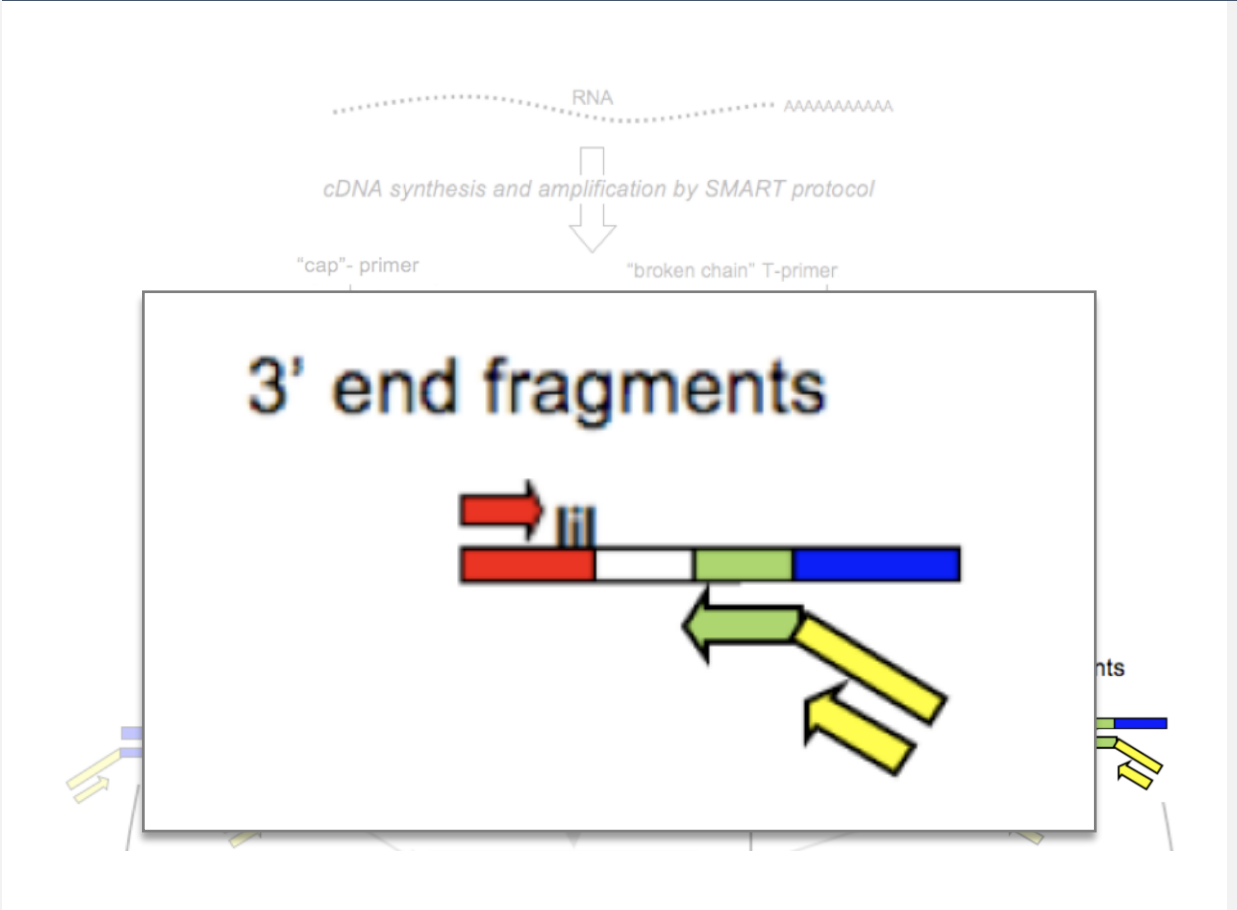


The Relevant Chemistry Is the Same in Figure 1 and Additional File 4

Figure 1



Additional File 4



No Evidence Additional File 4 Would Give Different Results

Decision Granting Institution

“Moreover, Meyer touts the method in Additional File 4 as an improvement over the one in Figure 1. Ex. 1006, 14, 19. Patent Owner does not argue, and we find no evidence to suggest, that this improved method would generate fewer reads of the 3' end fragments than the 16% reported in Meyer. Thus, the lack of enrichment data from Meyer's method in Additional File 4 is not fatal to Petitioner's challenge.”

Data From Additional File 4 Is Not Required to Prove Anticipation

Decision Granting Institution

“To the extent Patent Owner argues that the Petition must point to actual data from method in Additional File 4 to show enrichment, we disagree. ‘Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure.’ *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Here, Meyer, a prior art printed publication, enjoys the presumption of enablement. *In Re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012).”

No Evidence Additional File 4 Would Give Different Results



Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

"I think it's reasonable to believe that if you repeated it exactly with the modified protocol, ***you would get very similar and comparable results.*** However, I have not done that, and so I can't say that with any certainty."

No Evidence Additional File 4 Would Give Different Results



**Dr. Carlos
Bustamante**
Expert for Tecan

- "Q.** Do you have some reason to think that [if] Figure 1 results in overrepresentation of the 3' ends that additional file 4 results in less overrepresentation of 3' ends?
- A.** Well, I – sitting here today right now, I can't tell you if one would overrepresent more than the other, whether there would be overrepresentation. I think they are hoping this would help with the protocol. They've worked on this before so if I were interested in unbiased transcriptome sequencing of a non-model organism, I'd certainly consider using their protocol. May run protocols and see which one did better."

1

Both methods in Meyer would achieve the same result

2

The POSA would not second guess Meyer's data

Meyer's Disclosure Is Clear

16% > 10%

with a single C. A single copy of this 'broken-T' adaptor was found in 98,276 of the raw reads (16% of the total), slightly more than the expectation (~10%) based on average read length (232 bp) and assuming an average transcript size of 2,200 bp. This comparison suggests that the 3' ends of transcripts were well-represented in our dataset, confirming the effectiveness of this solution for overcoming the homopolymer problem. Another difficulty in 454

BMC Genomics



Research article

Open Access

Sequencing and de novo analysis of a coral larval transcriptome using 454 GSFx

Eli Meyer^{*1}, Galina V Aglyamova¹, Shi Wang¹, Jade Buchanan-Carter², David Abrego³, John K Colbourne², Bette L Willis³ and Mikhail V Matz¹

Address: ¹University of Texas at Austin, 1 University Station C0930, Austin, TX, 78712, USA, ²The Center for Genomics and Bioinformatics, Indiana University, 915 East Third Street, Bloomington, IN, 47405, USA and ³ARC-Center of Excellence for Coral Reef Studies, and School of Marine and Tropical Biology, James Cook University, Townsville, QLD, 4811, Australia

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Tecan Does Not Dispute Meyer's 16% Number

✓ 16% > 10%

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Dr. Meyer Stood By the Calculations in His Reference

Tecan's Sur-Reply

“Petitioner misconstrues testimony to incorrectly assert that Dr. Meyer disagrees with Tecan’s positions. Petitioner claims that Dr. Meyer contradicted Tecan by saying that he ‘obviously thought [the 10% calculation] was reasonable, and my co-authors agreed because we included it,’ and that he ‘stand[s] by the statement as written.’ Paper 47, 18-19. Petitioner never asked whether those numbers are reasonable for assessing enrichment. EX1126.0043:6-44:7. When Petitioner did ask Dr. Meyer whether he had enriched for the 3' fragments, Dr. Meyer explained that they did not have the data to make that assessment. EX1126.0178:10-179:2, 183:9-190:13. Dr. Meyer repeatedly explained that the estimate could not be used to assess enrichment. *Id.*”

Dr. Meyer Stood By the Calculations in His Reference



Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

Q. And in the middle of the paragraph you say, 'A single copy of this "broken-T" adaptor was found in 98,276 of the raw reads (16% of the total), slightly more than the expectation approximately (~10%) based on average read length (232 bp) and assuming an average transcript size of 2,200 bp.'

A. Correct.

Q. *That calculation was designed to demonstrate that you had resolved the underrepresentation of the 3' ends, right?*

A. *That's correct."*

Q. This calculation's reasonable, right?

A. *I obviously thought it was reasonable, and my co-authors agreed because we included it. There are nuances worth discussing about the statement, but I stand by the statement as written."*

Tecan Argues the Inputs to the 10% Expectation Are “Flawed”

$$\frac{\text{Average read length} \quad (232 \text{ bp})}{\text{Assumed average transcript size} \quad (2,200 \text{ bp})} = 10\%$$

The 232 Base Pair Numerator Is Correct



Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

Q. Before we talk about the denominator, I want to talk about the numerator, the 232.

A. Sure.

Q. That number is based on the data that you generated, right?

A. That's correct.

Q. And so ***that number is not an assumption***, right?

A. Correct.

Q. *You don't have any reason sitting here today to think that you should have used a different number* for the numerator, right?

A. Correct."

The 2200 Base Pair Denominator Is Correct



Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

- Q.** You don't have any reason sitting here today to use any other number; that's fair?
- A.** I'll - I'll just restate that if I were to use a different number, it would have to be based on a search of the current scientific literature, and I don't know what that number would be. So I don't know if it would be different or the same.
- Q.** Sitting here today, 2200 is as accurate a number as any other number, right?
- A.** ***I think it was a reasonable number for us to choose in 2009 when we wrote the paper, and that's really the only bar that one has to meet in writing a scientific paper.***

Dr. Bustamante's Estimate Shows Enrichment



Dr. Carlos
Bustamante
Expert for Tecan

- "**Q.** What percentage would be the more appropriate one to use as the expectation, Dr. Bustamante?
- A.** I would be hard-pressed given I don't have the actual data. I just have the published distributions, but ***my sense is it is perhaps closer to 13 or 14 percent***, but again, that's a guesstimate. I have – and I think nobody has given the data that they have actually produced a reasonable way to differentiate whether the value here is demonstrating overrepresentation at all. I think it's about what they would have expected to see and that's what they claim and move on."

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The POSA Would Not Question Meyer's 232 bp Numerator

Sequencing and de novo analysis of a coral larval transcriptome using 454 GSFx

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The POSA Would Not Question Meyer's 232 bp Numerator

Tecan's Sur-Reply

“Petitioner presents disjointed, contradictory arguments concerning what a POSA could infer from *Meyer's* gel reads. Petitioner argues that a POSA would have understood *Meyer's* average transcript length as being empirically derived from a gel and thus acceptable for assessing enrichment. Paper 47, 19-20. Yet Petitioner then argues that the gel reads would be too ‘imprecise’ to estimate the average fragment length. *Id.* Petitioner contradicts itself, exposing the flaws in its arguments. Either Dr. Sims is incorrect and the gel reads are too imprecise for calculating a baseline value, underscoring *Meyer's* lack of data. EX2038.¶251. Or the gel reads are acceptable, in which case a POSA would have understood the expected baseline to be approximately 16% since *Meyer* reported the average fragment length as between 300-400 bp. EX2038.¶¶266-269.”

Meyer Does Not Teach 300-400 bp as the Numerator

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dom fragments appropriate for 454 sequencing. This was accomplished by first preparing 5 µg of amplified, normalized cDNA in a 100-µl volume. The pooled sample was submerged in an icewater bath and sonicated using a Misonix S3000 (Misonix, NY, USA) in 30 sec bursts followed by 30 sec rests, with power set at 0.5–1 (18–30 W). Fragmented cDNA samples were evaluated by gel electrophoresis to visualize the effectiveness of the process. A range of different sonication durations were tested, and the 3 minute treatment selected because it produced fragments in the appropriate size range (ca. 300–400 bp).

Dr. Bustamante Says the Denominator "Is Probably Smaller" But Did Not Offer A Number



Dr. Carlos
Bustamante
Expert for Tecan

- "Q.** Do you have an opinion as to what number should be used for the denominator instead of 2200?
- A.** So ***I don't have an exact number for you*** but I do think it should be smaller than 2200 based on the actual distribution of the assemblies they saw and ***the fact that that's a number picked out for mammals***, so they really need a better number based on corals, which is part of what they were trying to get to, to be frank. ***I think the number is probably smaller than 22.***"

Tecan's Argument Relies On "Mammalian Transcript" Theory

Tecan's Sur-Reply

“Nor did Dr. Meyer recant his testimony (Paper 47, 20-21) that the average transcript length is based off a mammalian transcript, which is *not even the same phylum* as the coral sequenced in Meyer. EX1126.0045:12-19, 60:18-61:5. Rather the question was whether Drs. Matz and Meyer first encountered this number in a well-known textbook or from their general knowledge. EX1126.0061:6-62:1. This is of no consequence, let alone the ‘admission’ Petitioner claims it to be. Either way, it confirms what Dr. Bustamante repeatedly testified: a POSA would not have reasonably inferred enrichment based on a general assumption. EX2038.¶¶260-265, 270; EX1125.0413:1-416:2.”

Dr. Matz's "Mammalian Transcript" Theory Was Rejected By Dr. Meyer



Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

- Q.** Do you have an independent recollection of referring to this textbook?
- A.** I believe I said before, but if not, I'll say clearly that the reason for choosing that value of 2200 was based on verbal conversations between Dr. Matz and I, 16 years ago. ***You'll notice that in the paper, we do not provide a reference for the 2200 number, and that's because we were drawing it from general knowledge at the time.***
- Q.** ***It's your testimony that the 2200 number came from general knowledge at the time; is that right?***
- A.** ***Correct.***

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Dr. Eli Meyer

First Author of
Meyer Reference

Expert for Tecan

- “Q.** And the longer version that you are saying a reader would understand from this is that they would read this as assuming an average transcript size of 2200 base pairs, parentheses, based on the general knowledge that an average transcript size of **2200 base pairs is based on the average length of a mammalian transcript?**
- A.** ***I think your introduction of the term ‘mammalian transcript’ into that sentence is not necessarily something that we were relying on or that the reader would assume.*** The statement, as written, assuming an average transcript size of 2200 base pairs, without any qualifiers, I think the reasonable assumption – the reasonable interpretation, rather, of that sentence is that **this is a general average overall transcript length. We didn’t mention anything about mammals in that sentence.**

The POSA Would Not Second Guess Meyer

Tecan's Sur-Reply

“Petitioner’s position is even more absurd as it then also tries to argue that Dr. Bustamante ‘conceded that the POSA’s expectation for the number of 3’ end fragments would be “13 or 14%.” Paper 47, 2, 22. Dr. Bustamante testified that he could not provide an estimate because he did not ‘have the actual data.’ EX1125.0417:12-22. Dr. Bustamante offered a ‘guesstimate’ based on only the published distributions in Meyer’s Figure 2. *Id.* Petitioner ignores that Dr. Bustamante also testified that a POSA could not reasonably infer enrichment based on the 10% expectation and available data. EX1125.0415:1-416:2, 417:22-418:5.”

Dr. Bustamante's Estimate Shows Enrichment



Dr. Carlos
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A. I would be hard-pressed given I don't have the actual data. I just have the published distributions, but **my sense is it is perhaps closer to 13 or 14 percent**, but again, that's a guesstimate. I have – and I think nobody has given the data that they have actually produced a **16% > 13-14%** differentiate whether the value overrepresentation at all. I think it's about what they would have expected to see and that's what they claim and move on.”

Instituted Grounds ('012 Patent)

Claims Challenged	Invalidity	Prior Art
Independent Claim 1 Dependent claims 3, 5-8, 10-14, 16, 20-22	<i>Anticipated by</i>	Meyer (EX1006)
Dependent Claim 2 (genomic DNA)	<i>Obvious over</i>	Meyer (EX1006) Siebert (EX1007)
Dependent Claim 9 (additional limitation not disputed)	<i>Obvious over</i>	Meyer (EX1006) Kelley (EX1010)
Dependent Claims 15, 17-19 (Illumina/Ion Torrent)	<i>Obvious over</i>	Meyer (EX1006) Caruccio (EX1008) Bronner (EX1009)

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seconds, 72° C. for 1 minute) for 25 cycles. PCR products are purified using AMPure XP beads and analyzed with a 2100 Bioanalyzer (Agilent Technologies).
Sequencing and Data Analysis
Equal masses of each of the amplified libraries (above) are pooled and diluted to working concentrations according to manufacturer's recommendations. Single end sequencing reads of 100 nt length are obtained for libraries using a MiSeq System (Illumina). Raw sequencing data is processed using Illumina base calling software. Samples from the various time points are binned based on their unique 8 base code and mapped to a reference database. Based on the mapping characteristics, individual samples or a new pool of samples can be rerun on the sequencer to obtain greater read depth. Samples with poor gene coverage will be eliminated from the pool.
What is claimed is:
1. A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
a) obtaining a nucleic acid fragment ligated to a partial duplex adaptor, wherein the nucleic acid fragment comprises a nucleic acid sequence of interest, wherein the partial duplex adaptor comprises a first adaptor sequence, and wherein the partial duplex adaptor comprises a first strand and a second strand, wherein the first strand is longer than the second strand;
b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor, wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;
c) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor with a polymerase, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
d) amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;
e) annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
f) sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.
2. The method of claim 1, wherein the nucleic acid fragment comprises genomic DNA.
3. The method of claim 1, wherein the nucleic acid fragment comprises cDNA.
4. The method of claim 1, wherein the nucleic acid fragment comprises RNA.

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5. The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.
6. The method of claim 1, wherein the one or more oligonucleotides comprise more than one oligonucleotide, and wherein the second adaptor sequence is common to the more than one oligonucleotides.
7. The method of claim 1, wherein the first adaptor sequence, the second adaptor sequence, or both comprise barcode sequence.
8. The method of claim 7, wherein the barcode sequence is at least 8 nucleotides in length.
9. The method of claim 7, wherein the barcode sequence is 12 nucleotides in length.
10. The method of claim 1, wherein the obtaining comprises obtaining a plurality of nucleic acid fragments ligated to a partial duplex adaptor, wherein each partial duplex adaptor of each nucleic acid fragment of the plurality of nucleic acid fragments comprises a barcode, and wherein each barcode is unique.
11. The method of claim 1, wherein the nucleic acid fragment ligated to the partial duplex adaptor is double-stranded prior to step b).
12. The method of claim 11, further comprising denaturing the nucleic acid fragment ligated to the partial duplex adaptor prior to step b), thereby generating a single-stranded nucleic acid fragment comprising the nucleic acid sequence of interest ligated to the first adaptor sequence.
13. The method of claim 1, wherein the polymerase is a DNA polymerase.
14. The method of claim 1, wherein the first strand of the partial duplex adaptor is ligated to a 5' end of the nucleic acid fragment.
15. The method of claim 1, wherein the second strand of the partial duplex adaptor is ligated to a 3' end of the nucleic acid fragment.
16. The method of claim 1, further comprising fragmenting a nucleic acid, thereby generating a nucleic acid fragment; and purifying the nucleic acid fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a).
17. The method of claim 1, further comprising performing bridge amplification of the annealed strand after step e).
18. The method of claim 1, wherein the sequencing comprises use of four labeled reversible terminators.
19. The method of claim 1, wherein the sequencing comprises semiconductor sequencing.
20. The method of claim 1, further comprising fragmenting a nucleic acid, thereby generating a nucleic acid fragment; and performing end repair on the nucleic acid fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a).
21. The method of claim 1, wherein the nucleic acid fragment of the nucleic acid fragment ligated to the partial duplex adaptor in step a) is obtained by performing reverse transcription on an RNA fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a).
22. The method of claim 1, wherein each end of the nucleic acid fragment is ligated to a partial duplex adaptor.
* * * * *

IDT Exhibit 1001.0033

Paper 9 at 7-8, 33; Paper 41 at 55; EX1001

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Instituted Grounds ('108 Patent)

Claims Challenged	Invalidity	Prior Art
Independent Claim 1 Dependent claims 3, 5-10, 14-18	<i>Anticipated by</i>	Meyer (EX1006)
Dependent Claim 2 (genomic DNA)	<i>Obvious over</i>	Meyer (EX1006) Siebert (EX1007)
Dependent Claims 11, 12, 19 (Illumina/Ion Torrent)	<i>Obvious over</i>	Meyer (EX1006) Caruccio (EX1008) Bronner (EX1009)

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seconds, 72° C. for 1 minute) for 25 cycles. PCR products are purified using AMPure XP beads and analyzed with a 2100 Bioanalyzer (Agilent Technologies).

Sequencing and Data Analysis

Equal masses of each of the amplified libraries (above) are pooled and diluted to working concentrations according to manufacturer's recommendations. Single end sequencing reads of 100 nt length are obtained for libraries using a MiSeq System (Illumina). Raw sequencing data is processed using Illumina base calling software. Samples from the various time points are binned based on their unique 8 base code and mapped to a reference database. Based on the mapping characteristics, individual samples or a new pool of samples can be rerun on the sequencer to obtain greater read depth. Samples with poor gene coverage will be eliminated from the pool.

What is claimed is:

1. A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:

a) annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence, wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;

b) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first adaptor sequence with a polymerase, in the reaction mixture, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;

c) amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest; and

d) sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

2. The method of claim 1, wherein the nucleic acid sequence of interest comprises genomic DNA.

3. The method of claim 1, wherein the nucleic acid sequence of interest comprises cDNA.

4. The method of claim 1, wherein the nucleic acid sequence of interest comprises RNA.

5. The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

6. The method of claim 1, wherein the plurality of nucleic acid fragments comprises the first adaptor sequence, and wherein the first adaptor sequence is common to the plurality of nucleic acid fragments.

7. The method of claim 1, wherein the one or more oligonucleotides comprises more than one oligonucleotide, wherein the second adaptor sequence is common to the more than one oligonucleotide.

8. The method of claim 1, wherein the first adaptor sequence and/or the second adaptor sequence comprise a barcode sequence.

9. The method of claim 1, further comprising denaturing double-stranded nucleic acid fragments prior to step a).

10. The method of claim 1, wherein the polymerase is a DNA polymerase.

11. The method of claim 1, wherein the sequencing comprises the use of four labeled reversible terminators.

12. The method of claim 1, wherein the sequencing comprises semiconductor sequencing.

13. The method of claim 1, wherein the sequencing comprises nanopore sequencing.

14. The method of claim 1, wherein each of the plurality of nucleic acid fragments comprises the first adaptor sequence at a 5' end.

15. The method of claim 1, further comprising fragmenting nucleic acids prior to step a), thereby generating the plurality of nucleic acid fragments.

16. The method of claim 1, further comprising ligating the first adaptor sequence to a nucleic acid fragment in the plurality of nucleic acid fragments prior to step a), thereby generating the nucleic acid fragment comprising the first adaptor sequence.

17. The method of claim 1, wherein the amplified products comprise a 3' end with sequence complementary to a sequence on a surface.

18. The method of claim 17, further comprising annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface prior to step d).

19. The method of claim 17, wherein the surface is a surface of a flow cell.

* * * * *

IDT Exhibit 1002.0033

**'012 Patent Claim 21 Is
Anticipated by Meyer**

Tecan Proposes a Narrowing Construction to Avoid Anticipation of Claim 21

Claim 21: Method of claim 1, wherein nucleic acid fragment “is obtained by performing **reverse transcription on an RNA fragment**”

Tecan POR

“Under the proper construction of the claims, the '012 patent requires that nucleic acid fragments, including RNA fragments, be generated through fragmentation. *See supra*, Section IV.D.4. **Because Meyer discloses fragmentation after reverse transcription—and not before—Meyer fails to anticipate claim 21.**”

Strong Presumption Against Tecan's Proposed Construction

In re Katz, 639 F.3d 1303, 1324 (Fed. Cir. 2011)

“[T]here is a strong presumption against a claim construction that excludes a disclosed embodiment.”

Tecan's Narrow Construction Excludes All Embodiments

- 1 { DNA or mixed DNA from more than one organism. In one embodiment, the DNA fragments can be derived from RNA that has been converted to cDNA through a first strand synthesis reaction using any of the methods well known in the art for generating cDNA from an RNA template which can include, but is not limited to, combining the RNA with a primer (i.e. random primer), and reverse transcribing the RNA template with an RNA-dependent DNA polymerase. In one embodiment, the DNA fragments can be derived from RNA that has been converted to double stranded cDNA through a first and second strand synthesis reaction using any of the methods well known in the art.
- 2 { Fragmentation of the DNA to produce the DNA fragments can be achieved through any of the methods described herein for fragmenting nucleic acids which can include, but are not limited to, physical (i.e. sonication), and/or chemical (i.e. restriction enzyme treatment) fragmentation reactions.

Tecan's Narrow Construction Excludes All Embodiments

- 1 Individual cells are isolated from whole blood using a FACS cell sorter. The cells are suspended in 10 µl of Prelude Lysis solution (a component of NuGEN Technologies, One Direct system), resulting in lysis of the cell membrane while the nuclear membrane remains intact. Sixteen of the single cell suspensions are selected for expression profiling. Briefly, kit reagents are used as described by the manufacturer to generate first and second strand cDNA from the total RNA present in the lysate. Double stranded cDNA products are purified using Agencourt AMPure XP beads (Beckman Coulter Genomics).
- 2 Generation of Fragments with Ligated Forward Adapters Components from the NuGEN Ovation Ultralow Library System (NuGEN Technologies) are used to generate next generation sequencing libraries from each of the purified sample. Briefly, DNA is blunted and prepared for ligation under the standard end-repair reaction conditions described in the kit. Fragments are then ligated to the forward adapter only. As depicted in FIG. 2, ligation attaches the forward adapter to each end of each DNA fragment, leaving a single-strand nick on the opposite strand. Adapter fill-in will be performed, thus generating ligation products where complementary ends exist on each insert.

'012 Patent Claim 22 Is Anticipated by Meyer

Claim 22 Is Anticipated by Meyer

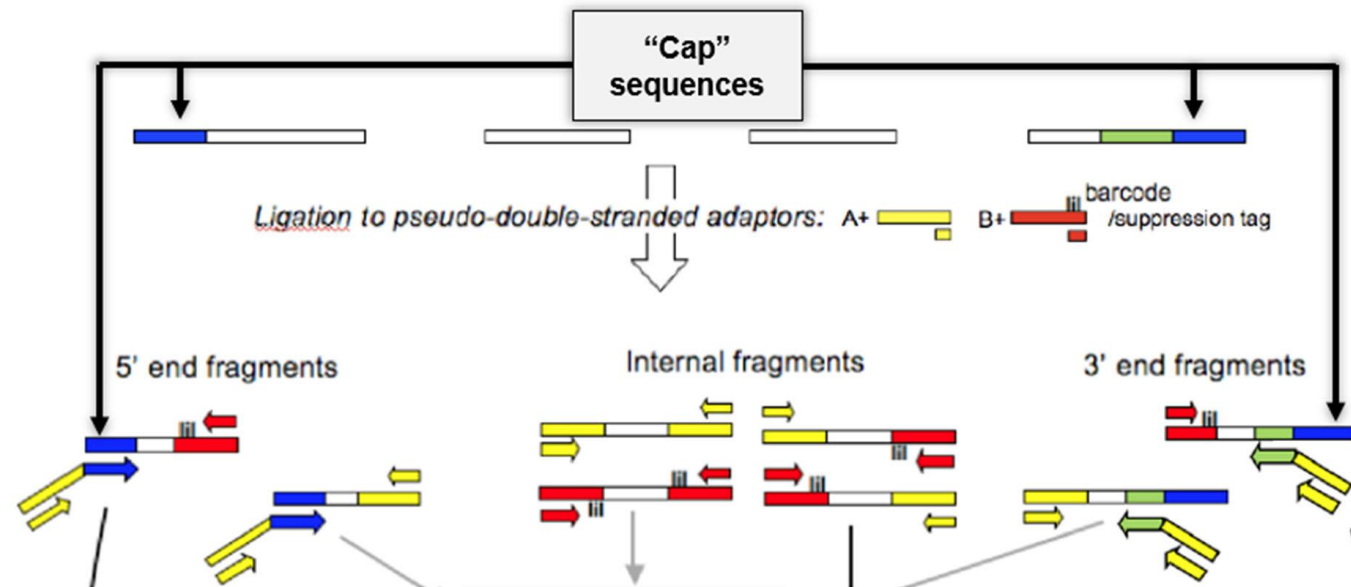
Claim 22: Method of claim 1, wherein “**each end of the nucleic acid fragment is ligated to a partial duplex adaptor**”

Meyer Teaches Ligation to Both Ends of Some Fragments



Dr. Peter Sims
Expert for IDT

“255. Claim 22 is anticipated by Meyer. As explained above, Meyer used the Clontech SMART cDNA kit to add a ‘cap’ sequence to the ends of the original cDNA molecules transcribed from mRNA prior to fragmentation. The 5’ ends of the cap sequence segments on the 5’ end fragments and 3’ end fragments were not phosphorylated. Therefore, for molecules with a complete cap sequence, the external ends of the 5’ end fragments and 3’ end fragments were ‘blocked’ from ligation. As shown in the below figure which I have reproduced in excerpted form and annotated from EX1006 (Meyer) at 0020, the only fragments that do not have partial duplex adaptors shown on both ends are fragments containing a fully intact cap sequence (‘3’ end fragments’ shown in the below figure), as the Cap Primer (blue), when intact, lacked the 5’ phosphates necessary for ligation. EX1006 (Meyer) at 0019-20. All ‘new’ 5’ ends generated during fragmentation, however, *did* contain 5’ phosphates and therefore were available for ligation to the partial duplex adaptors. EX1006 (Meyer) at 0019-20.”

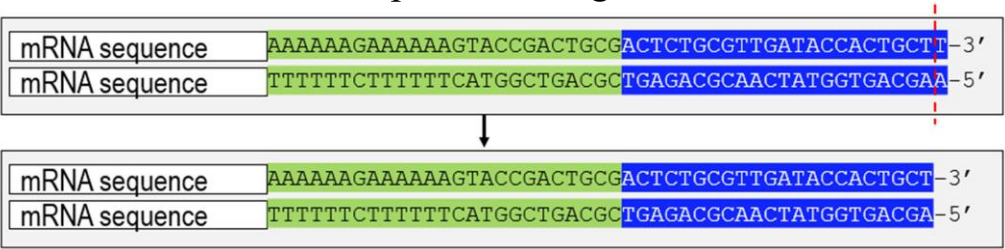


Meyer Teaches Ligation to Both Ends of Some Fragments

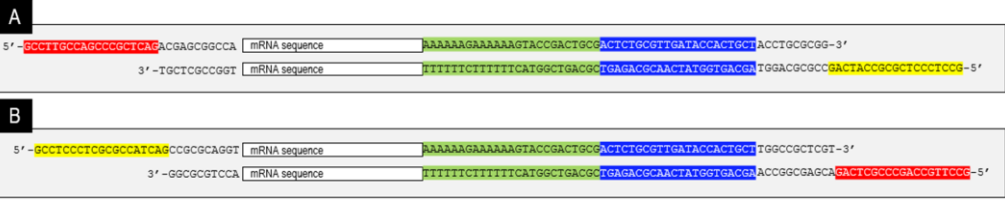


Dr. Peter Sims
Expert for IDT

“258. However, the POSA would understand that the Meyer figure is, like all ‘cartoon’ representations of complex chemical processes, oversimplified. It therefore depicts just one of many possible ‘3’ end fragment” variations—one in which the cap sequence remains fully intact. The POSA would understand that, because sonication is a random shearing technique, other variations of “3’ end fragments’ contained an incomplete cap sequence as a result of fragmentation occurring at any point *within* the cap region. One such variation is depicted below where one nucleotide was sheared from the end of the cap sequence. This fragment is only exemplary as fragmentation by sonication is a random process and could occur at any point, or multiple points in the fragment, and thus also within the blue cap sequence. While I have shown this fragment as an example, the POSA would understand that given the number of fragments in the Meyer sample and the random fragmentation method, multiple fragments were cleaved somewhere in the cap region and thus were then end-repaired and ligated.”



“259. For those ‘3’ end fragments’ containing only a portion of the cap sequence, a partial duplex adaptor ligated to both ends of the fragment, as the ‘new’ 5’ end within the cap region was phosphorylated during end repair. Therefore, many ‘3’ end fragments’ had partial duplex adaptors ligated to both ends. Two potential configurations of this (A and B) are depicted below.”



Meyer's Deposited Sequencing Data Confirms Ligation To Both Ends



Dr. Peter Sims
Expert for IDT

“262. The Meyer group’s contemporaneously deposited sequencing data contains thousands of sequencing reads with a portion of the cap sequence contained in the ‘3’ end fragments’ ligated to an adaptor sequence (corresponding to the bottom strand of the 3’ end fragments in the ‘B’ configuration) which could have occurred only if adaptors were ligated on both sides of the original fragment strands. EX1006.0016. The below figure shows the number of hits in the Meyer sequencing data for sequences containing other portions of the full cap sequence, from 5’ to 3’, starting with the full cap sequence (for which there are, as expected, 0 hits).”

B Sequence	Barcode/ suppression tag	[Portion of] Cap Sequence	Broken-Chain polyT Sequence	No. of Hits in NIH NCBI Database:
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	AAGCAGTGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 0
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	AGCAGTGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 147
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	GCAGTGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 169
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	CAGTGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 306
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	AGTGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 346
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	GTGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 402
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	TGGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 44
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	GGTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 21
GCCTTGCCAGCCCGCTCAG	ACGAGCGGCCA	GTATCAACGCAGAGT	CGCAGTCGGTACTTTTTCTTTTTT	- 141

Dr. Bustamante Concedes Ligation to Both Ends



Dr. Carlos
Bustamante

Expert for Tecan

Q. And you agree that the fragmentation protocol that Meyer uses doesn't exclude the ends of the strands in some way?

A. I would agree that it fragments randomly as we were discussing.

Q. *And you agree in the data that Meyer deposited that it did, in fact, happen?*

A. *In about 1 percent or something like that. It was a very minuscule number.*

Dr. Meyer Concedes Ligation to Both Ends



Dr. Eli Meyer

**First Author of
Meyer Reference**

Expert for Tecan

Q. And during sonication, there's nothing that prevents fragmentation within the blue cap sequence, right?

A. Correct.

Q. And if such a fragment is created, it's then end repaired and available for ligation, correct?

A. Correct. It should be.

Q. So while they're not drawn here, you could also end up with fragments that are sort of red or yellow adaptor, piece of the blue adaptor, orange adaptor, white adaptor, red or yellow adaptor?

A. I believe that's correct."



**It Would Have Been
Obvious to Adapt Meyer
to Genomic DNA**

Claim 2 Adds Only "Genomic" Source of DNA

'012 Patent Claim 2

2. The method of claim 1, wherein the nucleic acid fragment comprises **genomic** DNA.

'108 Patent Claim 2

2. The method of claim 1, wherein the nucleic acid sequence of interest comprises **genomic** DNA.

Meyer Method Was Performed on cDNA

BMC Genomics

Research article

Sequencing and de novo analysis of a coral larval transcriptome using 454 GSFx

Eli Meyer¹, Galina V Aglyamova¹, Shi Wang¹, Jade Buchanan-Carter², David Abrego³, John K Colbourne², Bette L Willis³ and Mikhail V Matz¹

Address: ¹University of Texas at Austin, 1 University Station C0930, Austin, TX, 78712, USA, ²The Center for Genomics and Bioinformatics, Indiana University, 915 East Third Street, Bloomington, IN, 47405, USA and ³ARC Centre of Excellence for Coral Reef Studies, and School of Marine and Tropical Biology, James Cook University, Townsville, QLD, 4811, Australia

Email: Eli Meyer - ElMeyer@mail.utexas.edu; Galina V Aglyamova - aglyamova@mail.utexas.edu; Shi Wang - swang@mail.utexas.edu; Jade Buchanan-Carter - jahuchan@indiana.edu; David Abrego - david.abrego@jcu.edu.au; John K Colbourne - jcolbour@cgh.indiana.edu; Bette L Willis - bette.willis@jcu.edu.au; Mikhail V Matz - matz@mail.utexas.edu

* Corresponding author

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Abstract

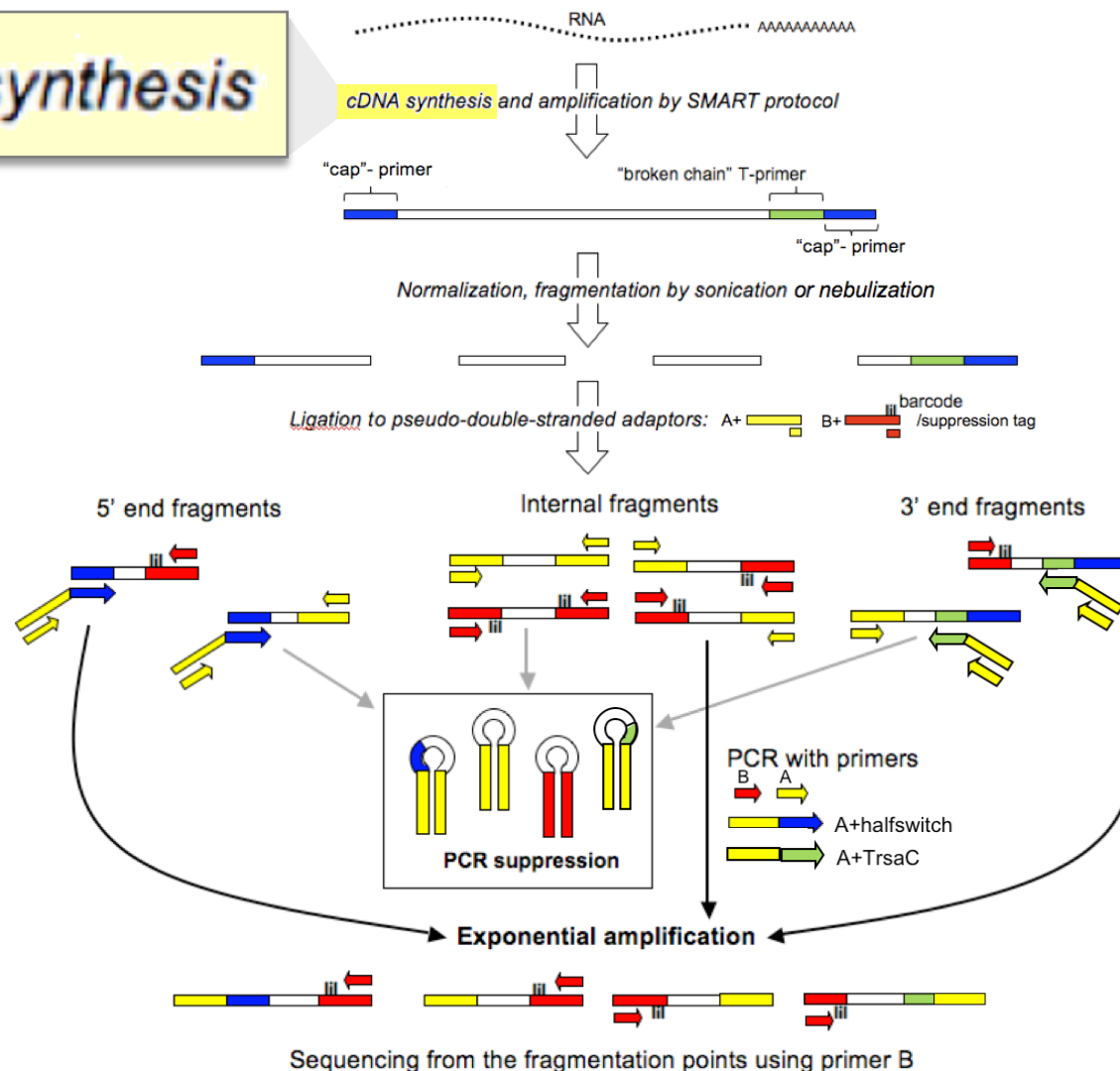
Background: New methods are needed for genomic-scale analysis of emerging model organisms that exemplify important biological questions but lack fully sequenced genomes. For example, there is an urgent need to understand the potential for corals to adapt to climate change, but few molecular resources are available for studying these processes in reef-building corals. To facilitate genomics studies in corals and other non-model systems, we describe methods for transcriptome sequencing using 454, as well as strategies for assembling a useful catalog of genes from the output. We have applied these methods to sequence the transcriptome of planulae larvae from the coral *Acropora millepora*.

Results: More than 600,000 reads produced in a single 454 sequencing run were assembled into ~40,000 contigs with five-fold average sequencing coverage. Based on sequence similarity with known proteins, these analyses identified ~11,000 different genes expressed in a range of conditions including thermal stress and settlement induction. Assembled sequences were annotated with gene names, conserved domains, and Gene Ontology terms. Targeted searches using these annotations identified the majority of genes associated with essential metabolic pathways and conserved signaling pathways, as well as novel candidate genes for stress-related processes. Comparisons with the genome of the anemone *Nematosella vectensis* revealed ~8,500 pairs of orthologs and ~100 candidate coral-specific genes. More than 30,000 SNPs were detected in the coral sequences, and a subset of these validated by re-sequencing.

Conclusion: The methods described here for deep sequencing of the transcriptome should be widely applicable to generate catalogs of genes and genetic markers in emerging model organisms. Our data provide the most comprehensive sequence resource currently available for reef-building corals, and include an extensive collection of potential genetic markers for association and population connectivity studies. The characterization of the larval transcriptome for this widely-studied coral will enable research into the biological processes underlying stress responses in corals and evolutionary adaptation to global climate change.

IDT Exhibit 1006.0001 Page 1 of 18
(page number not for citation purposes)

cDNA synthesis



cDNA and Genomic DNA Have Identical Chemistry



Dr. Peter Sims
Expert for IDT

“323. It would have been obvious to the POSA that the Meyer method, which uses cDNA, could easily be used with genomic DNA instead. Due to the identical chemistries of double-stranded cDNA and genomic DNA, the POSA would have had a high expectation of success in doing so, and would have been motivated by the teachings of Siebert and other ‘genome walking’ literature, EX1051 (Tonooka); EX1052 (Leoni), to adapt the teachings of Meyer for the context of genomic DNA.”

cDNA and Genomic DNA Have Identical Chemistry



**Dr. Carlos
Bustamante**
Expert for Tecan

Q. I could do the same chemistry on genomic DNA; right?

A. Depends on what you mean by the same chemistry. You couldn't do the cDNA synthesis for genomic DNA, could you?

Q. You can do the rest of the steps though; right?

A. You wouldn't - so the cap ends require you to leverage the cDNA chemistries so the end - I don't mean to question your molecular biology skills, I'm not sure how you would modify the protocol to put the caps on, if someone could or would, I don't know. **But you could certainly start with genomic DNA and fragmented genomic DNA."**

Prior Art Taught Similar Chemistry for Genomic DNA

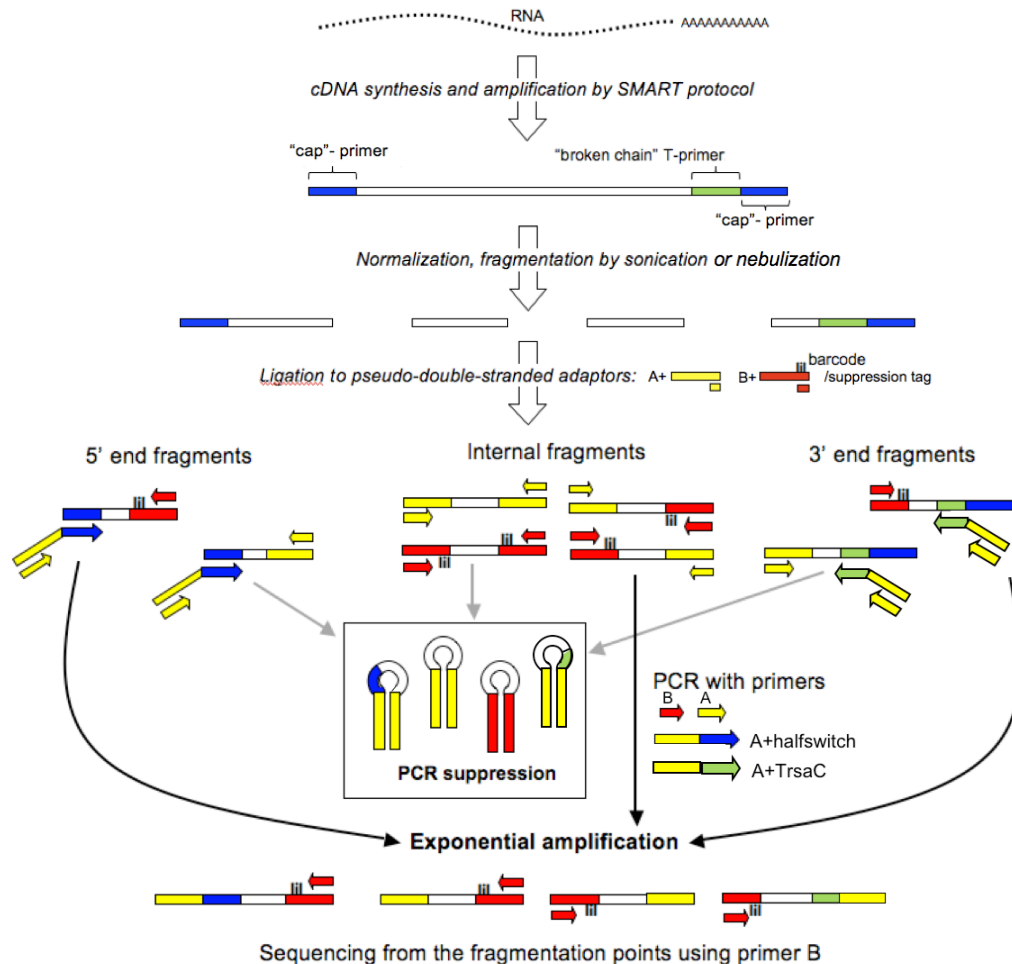


Dr. Peter Sims
Expert for IDT

“324. The concept of targeting a known genomic DNA sequence with a target-specific primer in order to obtain sequencing information regarding an unknown, adjacent genomic DNA sequence had been known in the art at least since the mid-1990s when Siebert described ‘[s]everal PCR-based methods’ that were already ‘available for walking from a known region to an unknown region in cloned or uncloned genomic DNA.’ EX1007 (Siebert) at 0001.”

Prior Art Taught Similar Chemistry for Genomic DNA

Meyer



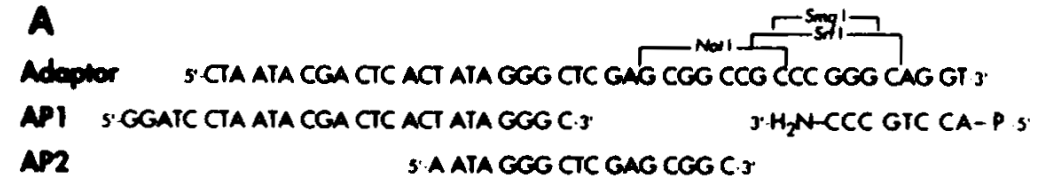
Siebert

A

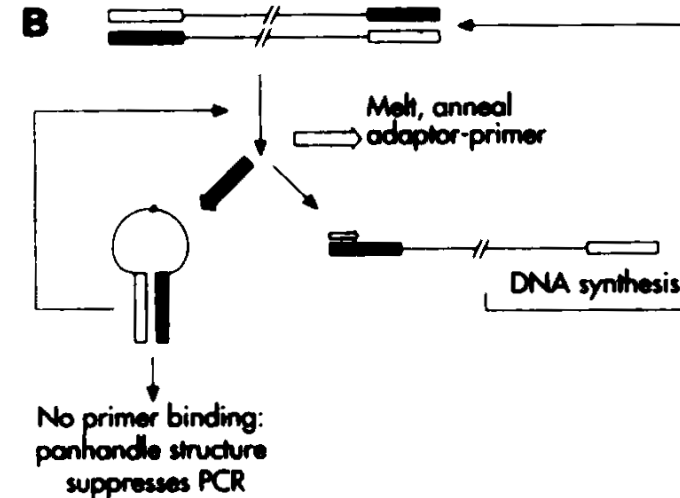
Adaptor

AP1

AP2

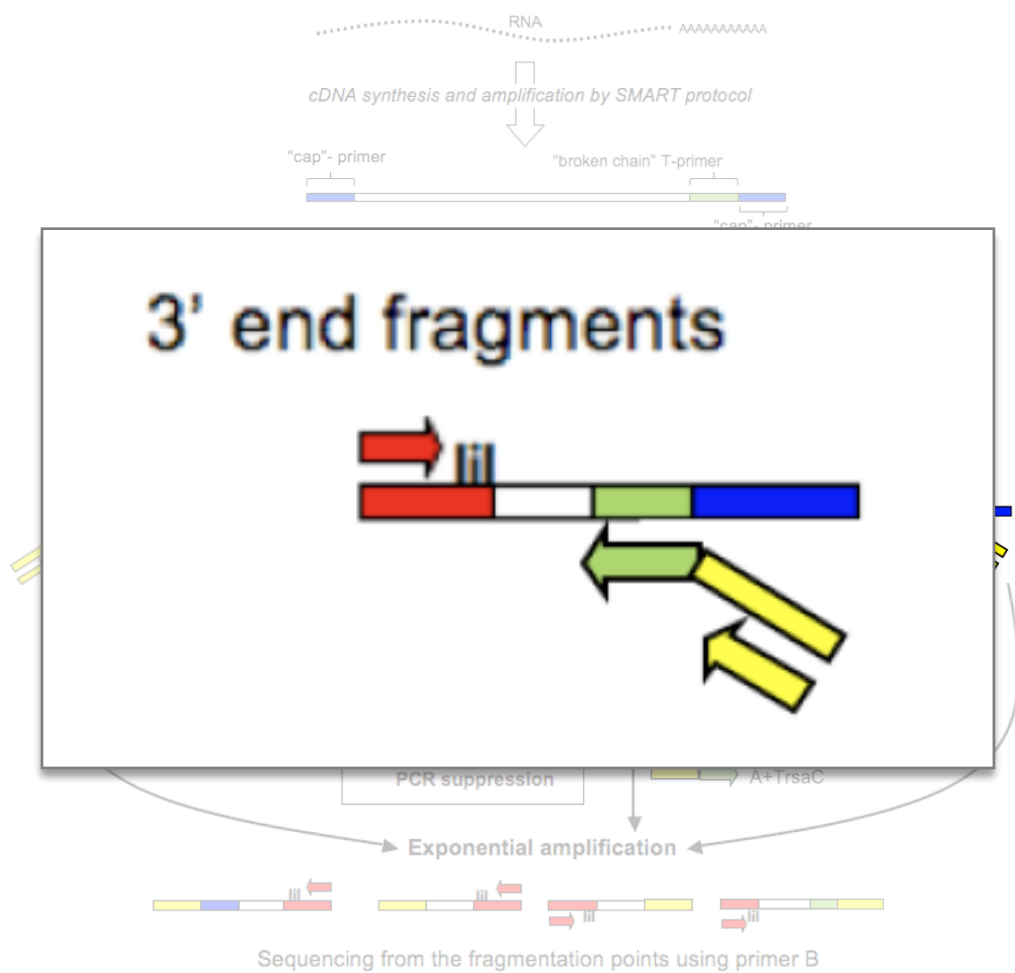


B



Prior Art Taught Similar Chemistry for Genomic DNA

Meyer



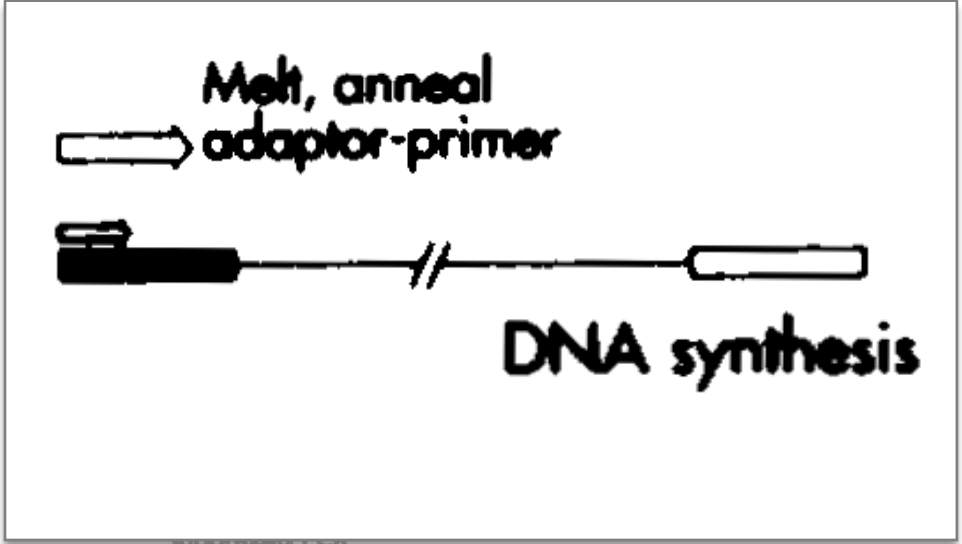
Siebert

A

Adaptor

AP1

AP2



Prior Art Provided Motivation to Combine Siebert and Meyer



The extreme flexibility of GW strategies makes its application possible in every standardly equipped research laboratory. In addition, the possibility of merging GW strategies to next generation sequencing approaches will undoubtedly extend the future application of this by now basic technique of molecular biology.

**It Would Have Been
Obvious to Adapt Meyer
to Other NGS Platforms**

Illumina and Ion Torrent Were Market Leaders at Priority Date



**Dr. Carlos
Bustamante**
Expert for Tecan

“92. Even before January 2012, Illumina dominated the market. *See* EX2060.0002 (‘As of this writing, Illumina dominates the market with 60% of the second-generation sequencer installations, while Life Technologies’ SOLiD system and Roche split nearly all of the remaining market at 19% each.’). J.P. Morgan estimated that while 454 sequencers made up almost 57% of the NGS market in 2007, it was expected to decline to less than 18% by 2012 as Illumina and Ion Torrent became more popular. EX2076.0042. One market survey around the time reported higher consumer dissatisfaction with the 454 sequencers.”

Illumina and Ion Torrent Were Market Leaders at Priority Date



Dr. Peter Sims
Expert for IDT

“As of the priority date, the ‘leading bench top sequencers currently available [were] Life Technologies [semiconductor] Ion Personal Genome Machine (PGM) and Ion Proton; and Illumina’s MiSeq sequencers.’ EX1009 (Bronner) at 2. Indeed, as of 2011, Ion Torrent’s semiconductor method was touted for ‘deliver[ing] unprecedented speed, scalability and low cost.’ EX1083 (Myers) at 0001-02.”

NGS Platforms Were Known to be Easily Interchangeable

Caruccio

Chapter 17

Preparation of Next-Generation Sequencing Libraries Using Nextera™ Technology: Simultaneous DNA Fragmentation and Adaptor Tagging by In Vitro Transposition

Nicholas Caruccio

Abstract

DNA library preparation is a common entry point and bottleneck for next-generation sequencing. Current methods generally consist of three steps: (1) shearing genomic DNA into small fragments, (2) end-repairing the fragments, and (3) ligating sequencing adaptors to the ends of the fragments.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

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End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

End-repairing and adaptor ligation can be performed sequentially, or they can be combined into a single step using a single enzyme.

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“Despite the diversity in sequencing chemistries used for sequencing polony arrays or single molecules, upstream sample preparation is generally very similar and follows a common three-step workflow. In the first step, large DNAs are sheared to appropriately sized fragments. Next, the DNA fragments are ‘repaired’ to have blunt ends or A tails. In the final step, platform-specific adaptors are ligated onto the repaired fragments in order to attach the library to a solid surface in a spatially separated array via a complementary sequence (e.g., a tagged glass slide or bead).”



Dr. Peter Sims
Expert for IDT

“Caruccio taught that the only step necessary for modifying an NGS library preparation method for use with one NGS platform to use with a different NGS platform was swapping out the ‘platform-specific adaptors’ ligated to the fragments. EX1008 (Caruccio) at 0002-03. This is consistent with my own experience.”

Tecan Failed to Show Nexus to Objective Indicia

Dr. Bustamante Performed the Wrong Legal Analysis

In re Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011)

“Evidence of secondary considerations must be **reasonably commensurate** with the scope of the claims . . . and provide[] an adequate basis to support the conclusion that **other embodiments falling within the claim will behave in the same manner.**”



**Dr. Carlos
Bustamante**
Expert for
Tecan

“Q. I don’t understand you to have such an opinion but do you, Dr. Bustamante, have any opinion as to whether the Ovation and Allegro embodiments that you identify are reasonably commensurate with the scope of the claims?”

A. I don’t recall being asked to prepare a section on whether they are commensurate.”

Tecan Did Not Ask Dr. Bustamante the Relevant Legal Question



**Dr. Carlos
Bustamante**
Expert for Tecan

- “Q.** Have you done any analysis or offered any opinions about what other embodiments fall within the scope of these claims?
- A.** Are you asking me about other products or are you asking me about other – what specifically are you asking me about in terms of other embodiments?
- Q.** Other products or other ways of using these methods.
- A.** The sections that I prepared for this declaration were the sections I was asked to prepare in connection with the strategy laid out by counsel.”

The Claims Are Not Coextensive With Tecan's Products

Tecan POR

“Tecan's Ovation and Allegro products are coextensive with the claimed methods. *Id.* The products also embody the unique SPET covered by the claimed methods.”



**Dr. Carlos
Bustamante**

Expert for
Tecan

“Q. The claims aren't limited to the embodiments that are the Ovation and Allegro products; right?

A. No, there can be other embodiments.”

Meyer Anticipates or Renders Obvious The Claims

1 Claim 1 is anticipated under the Board's construction of "enrich"



Every chemistry step of the claim occurs in Meyer



Meyer "adds or increases the proportion of" 3' end fragments compared to other fragments

2

Under Tecan's construction, Meyer showed enrichment



Meyer reports observing the sequence of interest in 16% of fragments, "slightly more" than would be expected from unbiased amplification (10%)



Dr. Meyer agreed the 10% and 16% were reasonable



Dr. Bustamante estimates the 10% should be "closer to 13 or 14%," **still less than the observed 16%**

3

Tecan's sur-reply construction should be rejected



Tecan's new limitation (precluding amplification of fragments not containing sequence of interest) **finds no support in the claims**



Impermissibly **limits the claim to Figure 1**



Contradicts Tecan's infringement interpretation of the claim

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on January 20, 2026, I caused a true and correct copy of the foregoing Petitioner's Demonstrative Exhibits to be served on counsel for Patent Owner via email at:

Timothy J. Beavers	tbeavers@goodwinlaw.com
Linnea P. Cipriano	lcipriano@goodwinlaw.com
John P. Padro	jpadro@goodwinlaw.com
Scott T. Weingaertner	sweingaertner@goodwinlaw.com
	dg-goodwintecan@goodwinlaw.com

Dated: January 20, 2026

Respectfully submitted,

/Thomas S. Fletcher/
Thomas S. Fletcher (Reg. No. 72,383)
WILLIAMS & CONNOLLY LLP
680 Maine Avenue SW
Washington, DC 20024
tfletcher@wc.com

*Lead Counsel for Petitioner
Integrated DNA Technologies, Inc.*