EXHIBIT 17

Illumina and PE Biosystems colluded to defraud Zip Code Inventors

Background and Chronology for Attempts by Illumina Employees to Re-Patent Zip Code Inventors Intellectual Property

Timeline for RICO Complaint

- January, 2018 – Illumina CEO Francis deSouza admits secret collaboration with Thermo Fisher "started the conversation clearly well over a year ago"… meaning prior to the April 2017 settlement agreement (see below). Discovery will reveal if this secret collaboration started over 3 years earlier in 2015, i.e. prior to the Markman and bulk of the *Cornell v Illumina* case (1:10-cv-00433-LPS).

- April, 2017 – Life Technologies (ThermoFisher) and Illumina fraudulently colluded to induce settlement of *Cornell v Illumina* in Delaware (1:10-cv-00433-LPS). This eventually was contested by a Rule 60(b)(6) Motion filed by Cornell once they became aware of Illumina's and ThrmoFisher's deception. This triggered a series of FOIA requests on Illumina SEC filings and NIH Grants in April and May 2017 by Plaintiff Zirvi.

- January, 2015 – Illumina in-house attorney, William Noon, files a highly unusual FOIA request to the NIH for copies of Illumina's own NIH SBIR Grants:
  - 1R21HG001911-01
  - 1R44HG002003-01
  - 1R43CA081952-01
  - 1R43CA083398-01

January 8, 2018 - Illumina unexpectedly announces collaboration with Thermo Fisher with a joint product: “Ampliseq for Illumina”.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15 (d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): January 8, 2018

Illumina, Inc.

(Exact name of registrant as specified in its charter)

But internal innovation is only part of the story. Our partnership strategy ensures that our customers will have access to best-in-class technology. With that in mind, I am very pleased to announce an exciting partnership with Thermo Fisher. This collaboration deeply integrates the leading and most trusted sequencers with the leading amplicon library prep technology. Thermo Fisher has 20 years of experience in PCR amplification chemistries that has enabled them to develop an amplicon library prep that is simple, fast and robust. The technology has been widely adopted in the oncology space because of the high-quality data achievable with low input and degraded samples, such as FFPE tissue.

But until now, those customers have not been able to take advantage of the accuracy and power of Illumina sequencers. This agreement provides direct access to AmpliSeq for our RUO customers, delivering the best of sequencing with the best amplicon protocol. Ahead of today's launch, we have been working together to adapt and optimize AmpliSeq specifically for Illumina sequencers, creating a seamless user experience that is fast and easy.

In addition to a collection of ready-to-order panels, Illumina customers will also be able to access AmpliSeq algorithms to create custom amplicon assays utilizing DesignStudio, our online assay design protocol, and they will have access to future panels and new assay types that are introduced as part of the AmpliSeq product line.

Amplicon sequencing is an important entry point for new NGS customers. The combination of our proven technologies further removes barriers to adoption, bringing more new-to-sequencing customers to our platform. Of course, we also have an installed base of more than 9,000 desktop systems. By giving our existing customers access to AmpliSeq chemistry, we're enabling them to do even more with their systems.

January 8, 2018 - Illumina CEO Francis deSouza admits secret collaboration with Thermo Fisher "started the conversation clearly well over a year ago"… meaning prior to the settlement agreement.

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Tycho W. Peterson - JP Morgan Chase & Co, Research Division - Senior Analyst

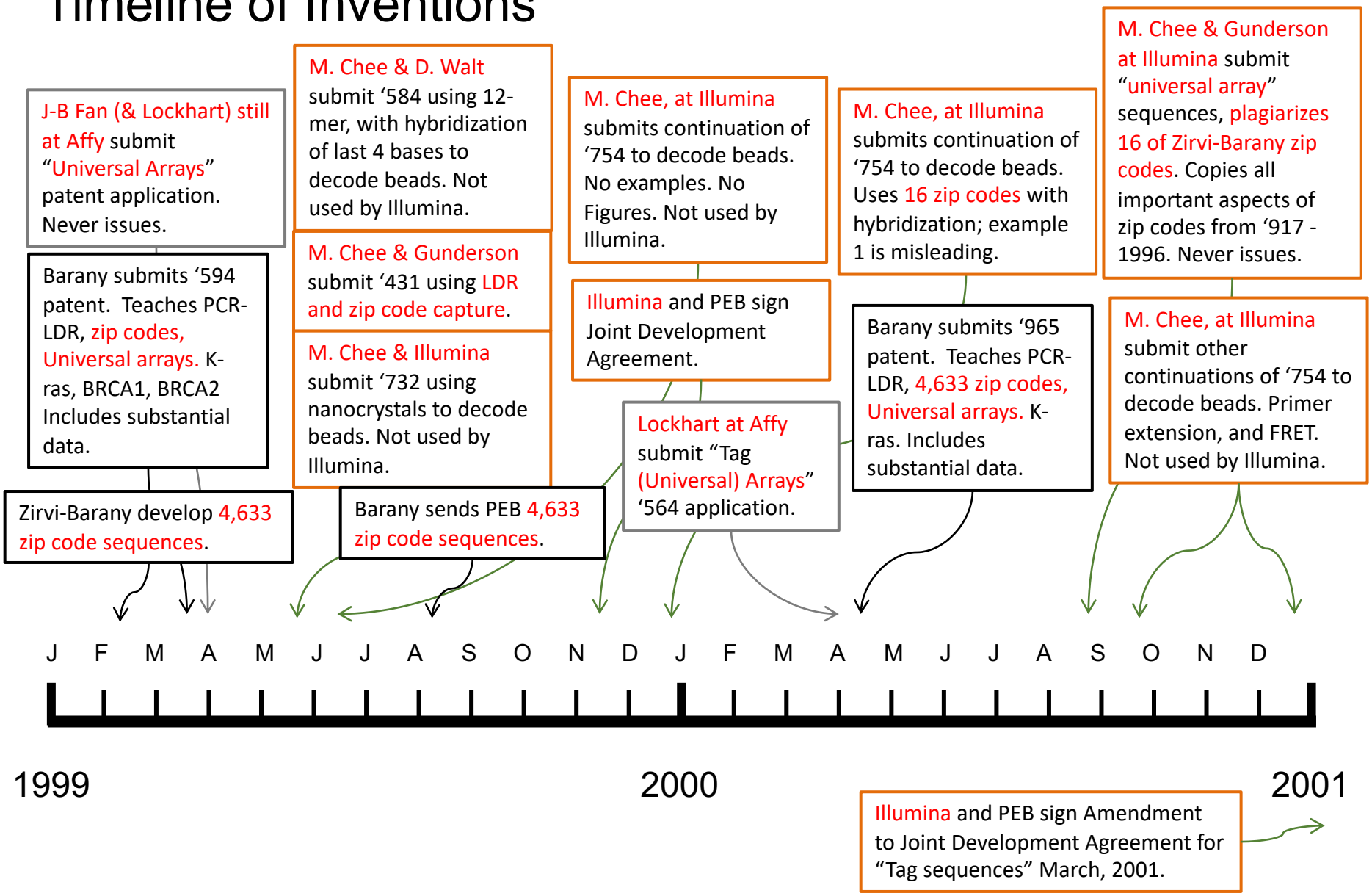
Can you talk about just that Thermo agreement, how that came about? (inaudible) press releases in Illumina (inaudible), so just a bit of speculation on that part? I mean, what's the back story?

Francis A. deSouza - Illumina, Inc. - CEO, President & Director

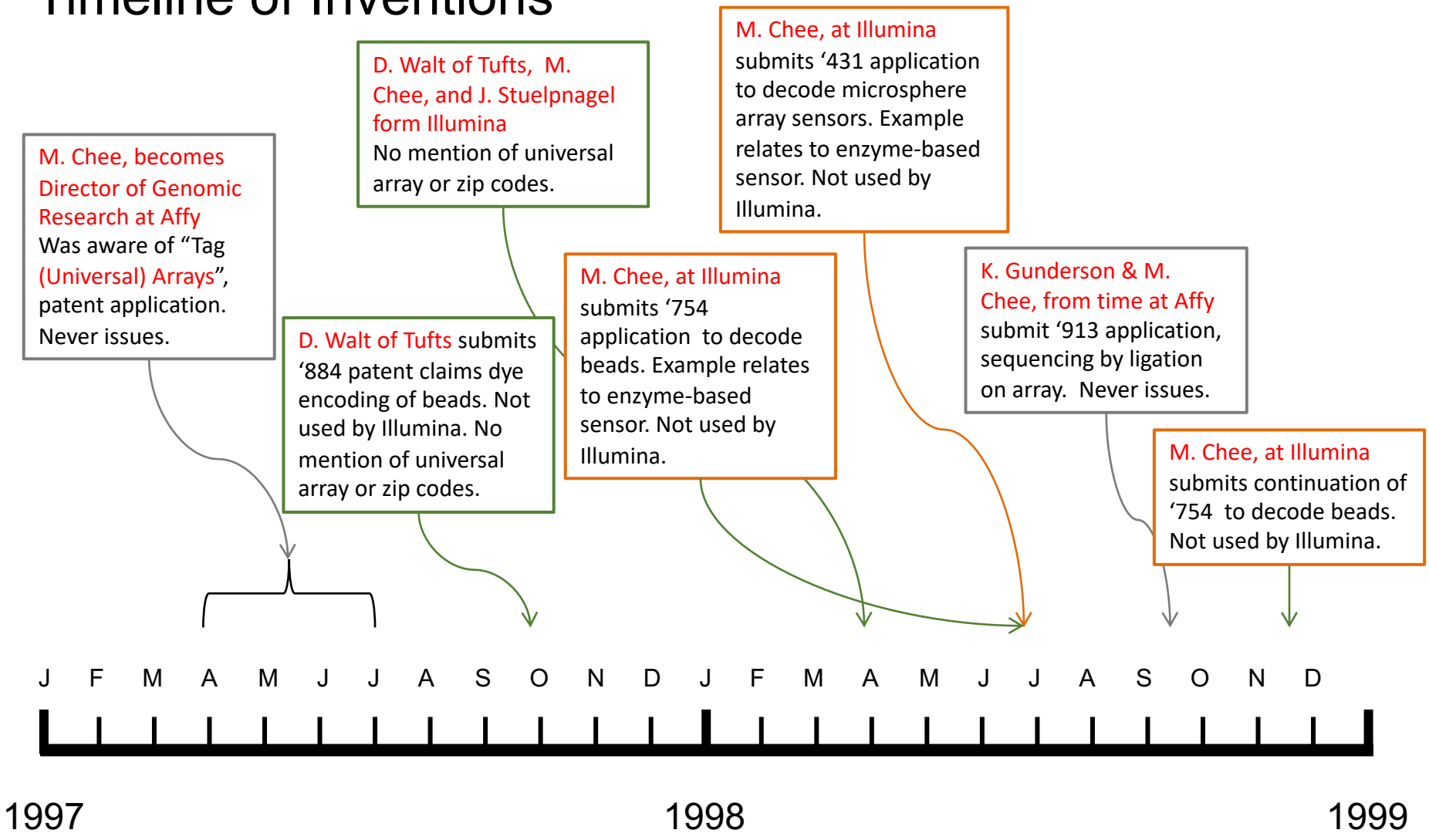
So the question is about the partnership we have with Thermo and what's the back story or how did that come about. The way it came about is as we talk to our customers around what they are looking for, one of the things that we heard consistently is that they liked certain aspects of AmpliSeq. And so they would tell us, look, they love the low sample they put in AmpliSeq, for example. They like the ability to work with degraded samples like FFPE tissue, and AmpliSeq has a following in the oncology community in terms of people like that assay. And so we spent a lot of time internally thinking, look, we want to make sure our customers have the best experience in our sequencer. So what is great for our customers is ultimately good for Illumina.

And so we started the conversation clearly well over a year ago. And initially, it was one of those, like, "Are you sure -- are we sure we want to do this? Are they sure they want to do this?" But it was always -- so the true north for us was what's the best thing for our customers? And if you keep looking at that, the truth is the best thing for our customers is to make the best amplicon technology available on the best sequencer. And I think a lot of credit on both sides. Thermo had the same thinking, which is, yes, there are parts of our portfolio we compete, but this is clearly good for AmpliSeq, it's good for customers and it's good for us. And so that was the thinking behind it. I think we're out of time.

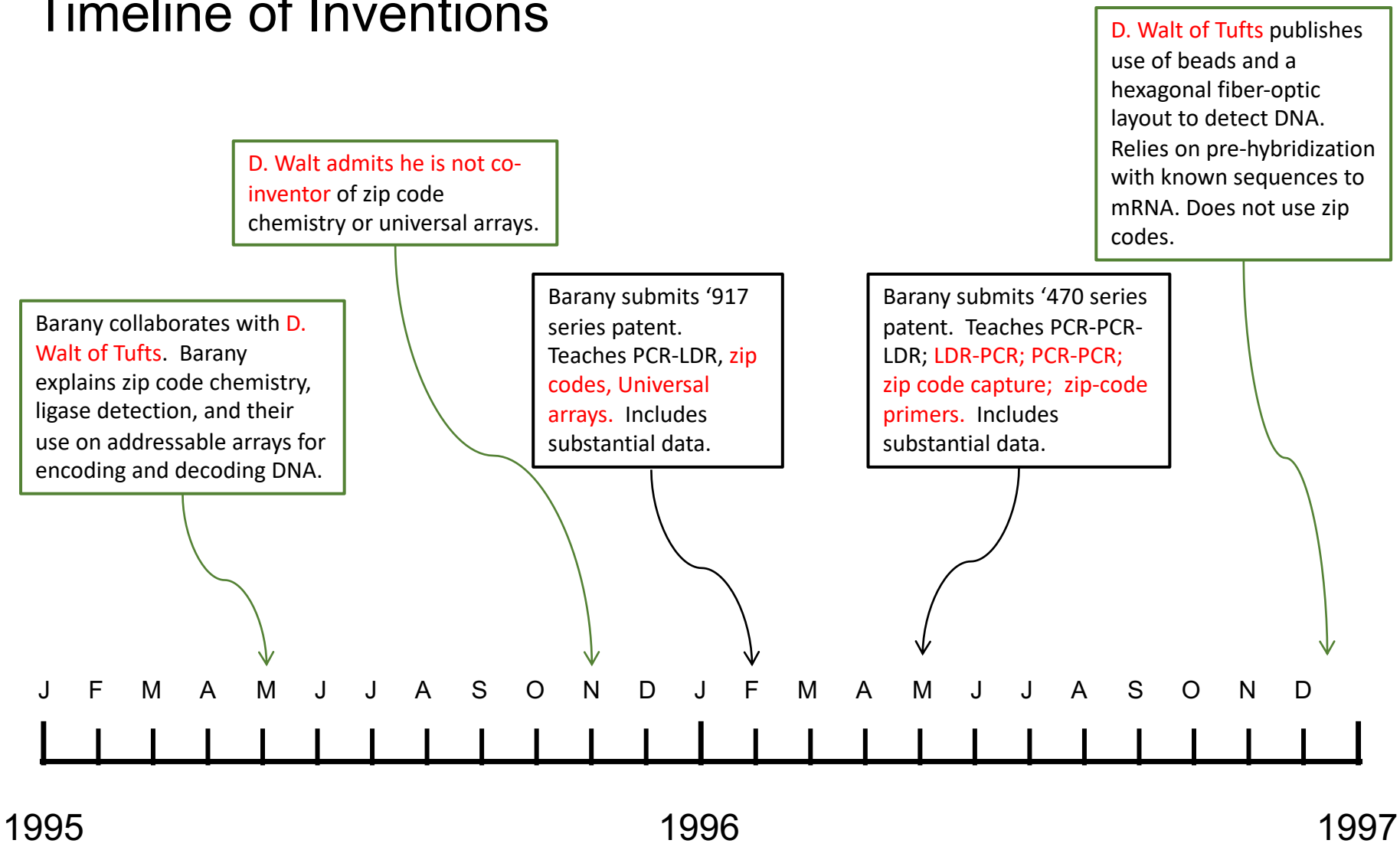
Timeline of Inventions



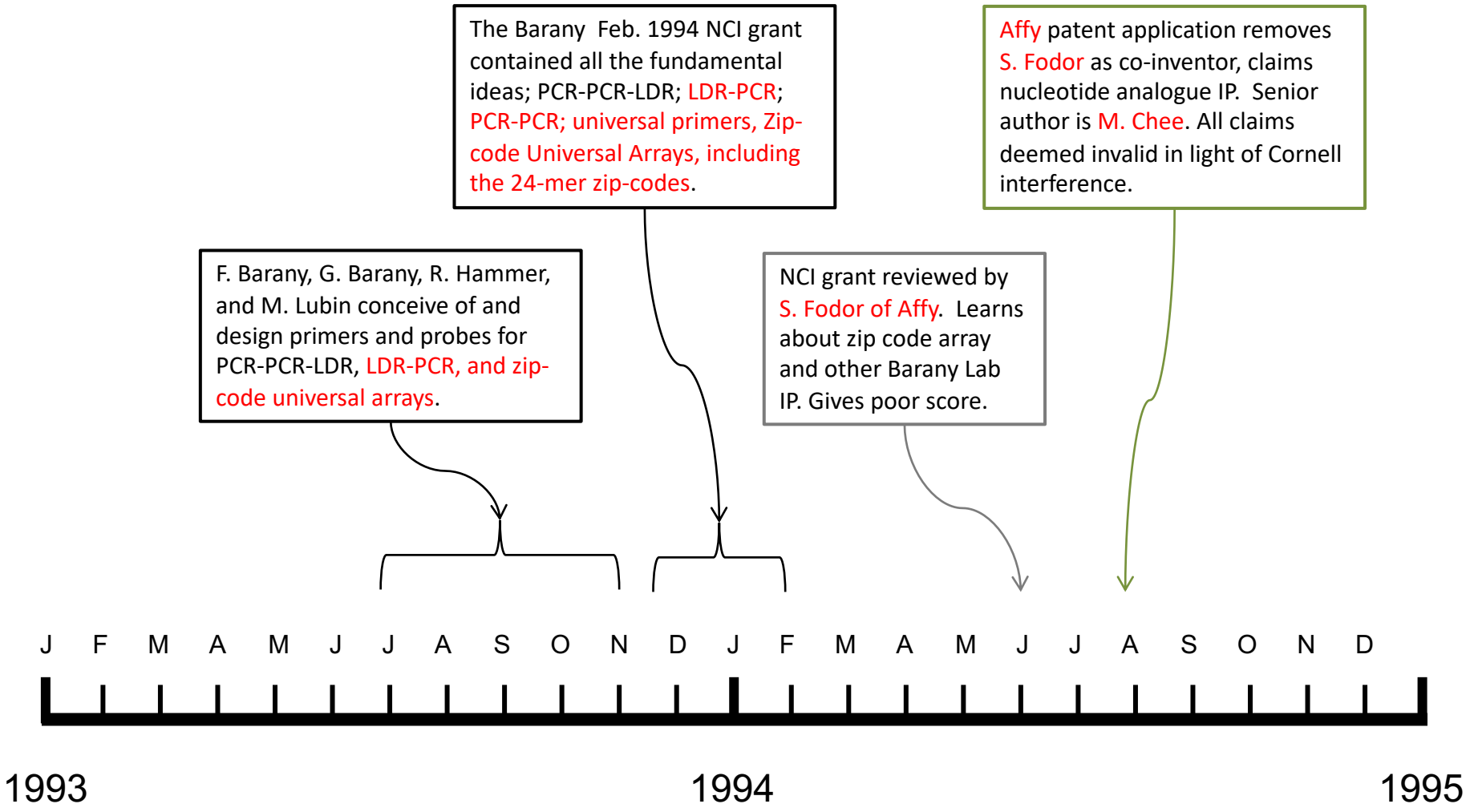
Timeline of Inventions



Timeline of Inventions



Timeline of Inventions



Concluding Remarks on the Timeline

1. Affymetrix employee Steve Fodor had *detailed knowledge* about the confidential Barany 1994 NCI grant submission, which described zip code chemistry, zip code primers, combining PCR with ligase detection reactions (LDR)and universal arrays.

2. David Walt, founder of Illumina (with Mark Chee and others, April 1998) reads draft of Barany's '917 patent application, and acknowledges to Mike Goldman on November 22nd, 1995 that he is ***not*** an inventor of zip code arrays.

3. Mark Chee, Kevin Gunderson, and J-B. Fan all worked at Affymetrix, and knew of zip code arrays *prior* to joining Illumina.

4. Affymetrix employees, including J-B. Fan, submit patent applications on March 26th, 1999, and April 6th, 2000 (as well as publications) using Universal arrays of 20-mer zip code sequences, they termed "Tag arrays" and "Tag Sequences".

5. David Walt and Mark Chee submit patent applications on May 20th, 1999, both for Illumina and Tufts describing other ways to encode for bead-arrays, i.e. nano-crystals, or sequencing by hybridization of 12-mers. In fact, Illumina failed to commercialize 7 of their own approaches for decoding which bead is in a given location.

6. Mark Chee, Kevin Gunderson, and J-B. Fan, submit several patent applications and publications using Universal arrays, with 24-mer zip codes AFTER the Nov. 9th, 1999 collaboration with ABI (PE-Biosystems) was announced.

7. Mark Chee and Kevin Gunderson had access to the confidential Zirvi-Barany *unpublished* 465 zip-code list – which was never published – from PEB some time between February 1999, (when Zirvi-Barany designed them and provided to PEB shortly thereafter,) and August 25th, 2000, when Illumina tried to re-patent Zirvi-Barany's zip codes.

8. Mark Chee and other Illumina employees file provisional application 60172106 on December 23rd, 1999 (claimed in both US7033754 and US7226734) where in Example 1, they claim to demonstrate identification of "16 zip codes" through 4 decoding steps, but knowingly and willfully conceal zip code sequences as well as hybridization and washing conditions used.

9. Mark Chee and Kevin Gunderson submit a patent application on August 25th, 2000 where they claimed to "generate a list of about 4,000 zip-codes, with special properties", which they call "Illumacodes" – such special properties were invented by Barany Lab in the '917 application of 1996. In Table 2, the first 16 zip codes are EXACTLY the same sequence as 16 of the first 52 Zirvi-Barany 24-mer zip-codes of the *unpublished* 465 list, and are in the identical order as that list, and *thus were plagiarized*.

Illumina and PE Biosystems Collaboration Requires Barany Lab's Zip Code Chemistry (covered by WO 97/31256 patent) for David Walt's Bead Arrays to Work

Joint Development Agreement, November 9th, 1999

JOINT DEVELOPMENT AGREEMENT

This Joint Development Agreement ("Agreement") dated as of the _____day of November, 1999 ("Effective Date") is by and between ILLUMINA, INC., a California corporation, located at 9390 Towne Centre Drive, Suite 200, San Diego, CA 92121- 3015 ("Illumina"), and PE CORPORATION, a Delaware corporation, through its PE Biosystems Group, located at 850 Lincoln Centre Drive, Foster City, CA 94404 ("PEB").

1.22. "Assembled Array" means an array of microspheres having chemical functionality attached thereto distributed on a patterned substrate, as generally described in U.S Patent Application No.08/818,199.

1.23. "Zip Code Chemistry" means a nucleic acid sequence detection method employing a sequence-specific hybridization pull-out step subsequent to a chemical or enzymatic polynucleotide ligation reaction, as generally described in International Patent Application No. WO 97/31256.

Illumina makes <u>randomly</u> "*Assembled* Arrays", invented by Dr. David Walt, while Dr. Francis Barany and team invented "Zip Code Chemistry" to make "*Addressable* Arrays" . On their own, randomly assembled bead arrays do not work for DNA analysis like SNP genotyping. The zip code chemistry of Barany Lab's IP not only works on traditional DNA arrays, but is also <u>the</u> enabling technology that allows the random bead arrays to work for DNA analysis.

Barany teaches Walt about ligation assays, zip codes, and Universal arrays:

Date: Mon, 1 May 1995 17:13:04 -0400
From: Francis Barany <barany@mail.med.cornell.edu>
To: dwalt@pearl.tufts.edu
Cc: barany@maroon.tc.umn.edu, chammer@sn01.sncc.lsu.edu,
dbergstr@mace.cc.purdue.edu, hjblok@mail.med.cornell.edu
Subject: Derivatized Glass

Dear David,

It was a pleasure to speak with you last week. You will be receiving a FedEx package from me some time this week which will include a confidential copy of our zip code approach, and some special glass slides for making the first test systems. These glass slides are a special thickness and will be used in a Perkin Elmer In-Situ PCR machine. I haven't received the slides yet, but as soon as I do, they will be sent to you.

I have discussed with my co-workers what type of functionality we would like on the polyethylene surfaces you can place on specific regions of glass using your optic fiber system. The early consensus is a COOH group so we can link it to our Amino-link oligonucleotides using water soluble carbocarbodi-imide activation. I'm not quite sure of the efficiency of this reaction, so I was wondering if you could make an activated group directly on your surface, so I could just react the amino-link oligo directly to your group. Perhaps you have some other suggestions. The COOH group will ultimately be used for building arrays using PNA oligomers on the surface.

I would also like to provide you with the phone numbers and E.mail addresses of the other collaborators on the zip code capture team:

Francis Barany, 212-746-6509, barany@mail.med.cornell.edu
George Barany, 612-625-1028, barany@maroon.tc.umn.edu
Donald Bergstrom, 317-494-6275, dbergstr@mace.cc.purdue.edu
Herman Blok, 212-746-6507, hjblok@mail.med.cornell.edu
Robert Hammer, 504-388-4025, chammer@sn01.sncc.lsu.edu

I'm looking forward to collaborating with you.

Francis

TUFTS UNIVERSITY

Department of Chemistry

November 22, 1995

Francis Barany, Ph.D.
Cornell University Medical College
Department of Microbiology
1300 York Avenue, Box 62
New York, NY 10021

Michael L. Goldman
Nixon, Hargrave, Devans & Doyle LLP
Clinton Square
Post Office Box 1051
Rochester, NY 14603-1051

Dear Francis:

Thank you for sending a copy of the patent DETECTION OF SINGLE BASE DIFFERENCES USING THE LIGASE DETECTION REACTION WITH ADDRESSABLE ARRAYS for my review. After going through the patent, we have found several protocols and/or references to work that my laboratory has contributed. Since we are not inventors on the patent we respectfully ask that any work that we have contributed to the patent be removed. Because we use these techniques in much of our research we do not wish to limit the scope of interest to which we can apply these techniques. Here is a list of places in the patent that we feel should be deleted:

pg. 25, line 34 - pg. 28, line 2
pg. 31, line 19
pg. 31, line 35
pg. 53, line 25 - pg. 55, line 26
pg. 56, line 36 - pg. 57, line 2
claims 33, 84, 110, 130 remove 3-aminopropyl methacrylate amide
claims 34, 85, 111, 131 remove 2-hydroxyethyl methacrylate
remove claims 115
delete Figures 20, 21

Thank you for your understanding in this matter. Please contact me if you have any questions.

Sincerely,

David R. Walt

62 Talbot Ave.
Medford, Massachusetts 02155
Telephone (617) 627-3441
Facsimile (617) 627-3443

David Walt admits that he did not invent zip codes and Universal arrays.

Illumina and PE Biosystems Collude to Defraud Zip Code Inventors

First Amendment to Joint Development Agreement, March 27th, 2001

Recitals

The parties have entered into a Joint Development Agreement ("Original Agreement") having an Effective Date of November 8, 1999.

This First Amendment, entered into pursuant to Section 13.7 of the Original Agreement, serves to amend the Original Agreement by providing for the development and commercialization of Tag Sequence technology.

CONFIDENTIAL TREATMENT REQUESTED

2. Add new Section 1.33 immediately after Section 1.32 of the Original Agreement as follows:

1.33 "Tag Sequence" means a set of oligonucleotide probes, developed pursuant to the Original Agreement or this First Amendment, which act independently of any target-sequence-specific analytical chemical reactions to allow the physical addressing of the products of a chemical reaction to locations on a solid support, such as the "addressable array-specific portion" of the oligonucleotide probes and their complements described in International Patent Application No. WO97/31256, and that are designed for use in the Collaboration Product. The Parties will agree on the selection Tag Sequences to be used in the Collaboration Product, subject to the approval of the Joint Steering Committee.

***

Illumina and PE Biosystems, deliberately colluded to provide "for the development and commercialization of Tag Sequence technology", which is really the "Zip Code Chemistry" invented in the Barany Lab. There is one and only one logical reason to redact the definition of "Tag Sequence" in this SEC document: To prevent the true inventors from finding out that Illumina and PE Biosystems were colluding to develop and commercialize sequences that infringed on the inventor's intellectual property. This was part of a deliberate strategy to re-name the inventors's zip codes with other names to obfuscate their origin.

First Amendment to Joint Development Agreement, March 27th, 2001

3. Add the following to Section 3.1 of the Original Agreement immediately before the last sentence of Section 3.1:

The Parties will share responsibility for defining and developing Tag Sequences for the Collaboration Product which will attempt to avoid third party intellectual property rights or other encumbrances.

4. Add new Sections 4.1.5 and 4.1.6 immediately after Section 4.1.4 of the Origina Agreement as follows:

4.1.5 Manufacture of Tag Sequences. It is understood that the Tag Sequences comprise complementary sets of oligonucleotides, one set of which will reside on the Assembled Arrays, and a second, complementary set which will be provided as part of the Reagents. In the Collaboration Field, Illumina will manufacture Tag Sequences for the Assembled Arrays and for use in decoding arrays; and PEB will manufacture Tag Sequences for the Reagents.

CONFIDENTIAL TREATMENT REQUESTED

***

Further, Illumina and PE Biosystems, deliberately colluded to develop "Tag Sequences for the Collaboration, which will attempt to avoid third party intellectual property rights or other encumbrances", in other words, to defraud the rightful inventors of royalties for the "Zip Code Chemistry". As this sentence was (accidentally) left un-redacted, when we asked about this section, Dr. Barany were falsely told by the lawyers that this did not refer to the true inventors intellectual property. The redacted section (4.1.5) clearly shows that Illumina and PE colluded to divide the responsibilities for manufacturing Tag sequences on assembled arrays (Illumina) and Tag sequences for reagents (PE). Since Tag sequences are synonymous to zip codes (section 1.33), uncovering this redacted section demonstrates that Illumina knew all along that zip codes work on both the array and in solution.

First Amendment to Joint Development Agreement, March 27th, 2001

5. **Add new Section 6.1.4 immediately after Section 6.1.3 of the Original Agreement as follows:**

6.1.4. **The Parties agree that any Intellectual Property Rights concerning Tag Sequences conceived after the Effective Date of the Original Agreement, whether Collaboration PEB Intellectual Property, Collaboration Joint Intellectual Property, or Collaboration Illumina Intellectual Property, including the methods by which such Tag Sequences are designed, selected or made, as well as any compositions directed to such Tag Sequences, shall be deemed Collaboration Joint Intellectual Property.**

The Parties, through their authorized officers, have executed this First Amendment as of the First Amendment Date.

ILLUMINA, INC.	PE CORPORATION (NY), THROUGH ITS APPLIED BIOSYSTEMS GROUP
By: John R. Stuelpnagel	By: Elaine J. Heron
Name: John R Stuelpnagel	Name:
Title: Vice President, Business Development	Title: Vice President, Applera Corporation General Manager, Molecular Biology Divisi Applied Biosystems
Date: 4/2/01	Date: 3/29/01

Illumina and PE Biosystems, deliberately colluded to jointly own “any Intellectual Property rights concerning Tag Sequences”,… “including the methods by which such Tag Sequences are designed, selected or made, as well as any compositions directed to such Tag sequences.” In other words, Illumina and PE Biosystems acknowledge the high value of “Tag sequences”, which per the redacted section 1.33 “Tag sequences mean” is really the intellectual property of WO97/31256, i.e. the “Zip Code Chemistry” invented by the Barany Lab.

Illumina's GoldenGate Assay and Tag Sequences Infringe on the Zip Code inventors Intellectual Property

Illumina – PE-Biosystems settlement agreement, August 18th, 2004

*CONFIDENTIAL
TREATMENT REQUESTED*

EXHIBIT 1

Description of the GoldenGate™ Assay

Illumina's GoldenGate™ assay involves all of the following steps:

Hybridization of at least two oligonucleotide probes to a target nucleic acid material, where the target material may be DNA, cDNA, RNA, or artificial oligonucleotide template;

Extension and ligation of one probe to the other while the probes are hybridized to the target material;

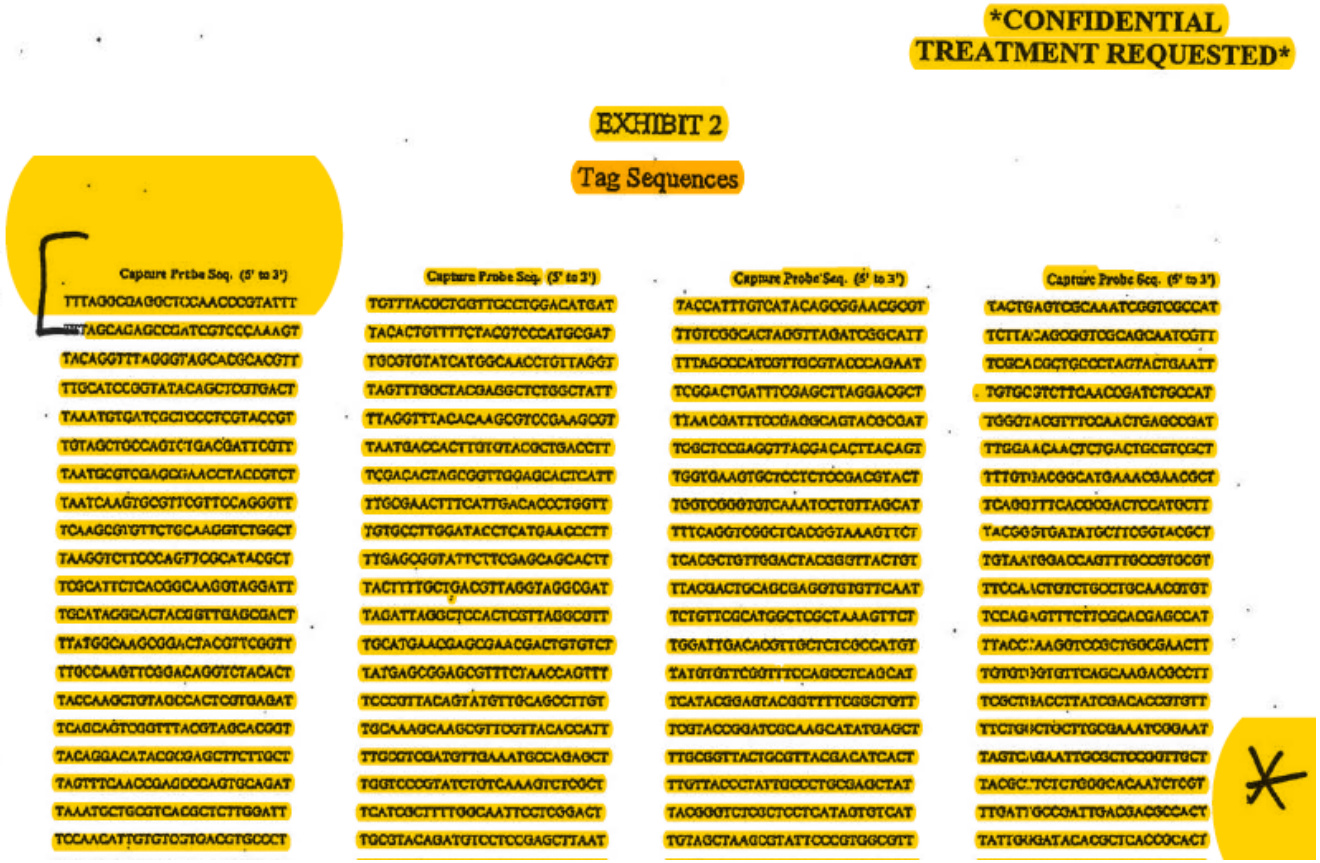
Eluting the extended and ligated probes from the target material;

Universal PCR, rolling circle, random priming, T4/Eberwine, strand displacement, TMA (transcripted mediated amplification), LCR (ligase chain reaction), MDA (multiple displacement amplification) or SPIA amplification of the extended and ligated probes to generate labeled amplicons; and

Detection of the amplicons on an Illumina BeadArray.

In this redacted section, Illumina admits that their "GoldenGate™" assay, uses Barany's LDR-PCR-Zip Code Chemistry technology, which is covered in the '917, '470, and '293 series patents. Again, the rightful inventors were harmed by deliberately redacting this section. Thus, Illumina deliberately set out to defraud the true inventors of royalties due from patents and trade secrets covering Barany's "Zip code chemistry", "Ligase Detection", and "Addressable Arrays" inventions.

Illumina – PE-Biosystems settlement agreement, August 18th, 2004



*CONFIDENTIAL
TREATMENT REQUESTED*

EXHIBIT 2

Tag Sequences

Capture Probe Seq. (5' to 3')	Capture Probe Seq. (5' to 3')	Capture Probe Seq. (5' to 3')	Capture Probe Seq. (5' to 3')
TTTAGGCGAGGCTCCAACCCGTATTT	TGTTTACGCTGGTTGCCTGGACATGAT	TACCATTTGTCATACAGGGGAACGCGT	TACTGAGTCGCAAATCGGTCGCCAT
TAGCAGCAGCCGATCGTCCCAAAGT	TACACTGTTTTCTACGTCCCATGCGAT	TTGTCGGCACTAGGTTAGATCGGCATT	TCTTACAGGGGTCGCAGCAATCGTT
TACAGGTTTAGGGTAGCACGCACGTT	TGCGTGTATCATGGCAACCTGTTAGGT	TTTAGCCCATCGTTGCGTACCCAGAAT	TCGCACGCTGCCCTAGTACTGAATT
TTGCATCCGGTATACAGCTCGTGACT	TAGTTTGGCTACGAGGCTCTGGCTATT	TCGGACTGATTTCGAGCTTAGGACGCT	TGTGCGTCTTCAACCGATCTGCCAT
TAAATGTGATCGCTCCCTCGTACCGT	TTAGGTTTACACAAGCGTCCGAAGCGT	TTAACGATTTCCGAGGCAGTACGCGAT	TGGGTACGTTTCCAACTGAGCCGAT
TGTAGCTGCCAGTCTGACGATTCGTT	TAATGACCACTTGTGTACGCTGACCTT	TCGCTCCGAGGTTAGGACACTTACAGT	TTGGAACAACTCTGACTGCGTCGCT
TAATGCGTCGAGGTAACCTACCGTCT	TCGACACTAGCGGTTGGAGCACTCATT	TGGTGAAGTGCTCCTCTCCGACGTACT	TTTGTTACCGCATGAAACGAACGCT
TAATCAAGTGCGTTCGTTCCAGGGTT	TTGCGAACTTTCATTGACACCCTGGTT	TGGTCGGGTGTCAAATCCTGTTAGCAT	TCAGGTTTCACCGGACTCCATCCTT
TCAAGCGTGTTCTGCAAGGTCTGGCT	TGTGCCTTGGATACCTCATGAACCCTT	TTTCAGGTCGGCTCACGGTAAAGTTCT	TACGGGTGATATGCTTCGGTACGCT
TAAGGTCTTCCCAGTTCGCATACGCT	TTGAGGGGTATTCTTCGAGCAGCACTT	TCACGCTGTTGGACTACGGGTTACTGT	TGTAATGGACCAGTTTGCCGTCCGT
TCGCATTCTCACGGCAAGGTAGGATT	TACTTTTGCTGACGTTAGGTAGGCGAT	TTACGACTGCAGCGAGGTGTGTTCAAT	TTCCAACTGTCTGCCTGCAACGTGT
TGCATAGGCACTACGGTTGAGCGACT	TAGATTAGGCTCCACTCGTTAGGCGTT	TCTGTTCGCATGGCTCGCTAAAGTTCT	TCCAGAGTTTCTTCGCACGAGCCAT
TTATGGCAAGCGGACTACGTTCGGTT	TGCATGAACGAGCGAACGACTGTGTCT	TGGATTGACACGTTGCTCTCGCCATGT	TTACCTAAGGTCCGCTGGCGAACTT
TTGCCAAGTTCGGACAGGTCTACACT	TATGAGCGGAGCGTTTCTAACCAGTTT	TATGTGTTCGGTTTCCAGCCTCAGCAT	TGTGTTGTGTTCAGCAAGACGCCTT
TACCAAGCTGTAGCCACTCGTGAGAT	TCCCGTTACAGTATGTTGCAGCCTTGT	TCATACGGAGTACGGTTTTCGGCTGTT	TCGCTTACCTTATCGACACCGTGTT
TCAGCAGTCGGTTTACGTAGCACGGT	TGCAAAGCAAGCGTTCGTTACACCATT	TCGTACCGGATCGCAAGCATATGAGCT	TTCTGTCTCCTTGCGAAATCGGAAT
TACAGGACATACGCGAGCTTCTTGCT	TTGCGTCGATGTTGAAATGCCAGAGCT	TTGCGGTTACTGCGTTACGACATCACT	TAGTCAGAATTGCGCTCCGGTTGCT
TAGTTTCAACCGAAGCCCAGTGCAGAT	TGGTCCCGTATCTGTCAAAGTCTCGCT	TTGTTACCCTATTGCCCTGCGAGCTAT	TACGCTCTCTGGGCACAATCTCGT
TAAATGCTGCGTCACGCTCTTGGATT	TCATCGCTTTTGGCAATTCCTCGGACT	TACGGGTCTCGCTCCTCATAGTGTCAT	TTGATTGCCGATTGACGACGCCACT
TCCAACATTGTGTCGTGACGTGCCCT	TGCGTACAGATGTCCTCCGAGCTTAAT	TGTAGCTAAGCGTATTCCCGTGGCGTT	TATTGCGATACACGCTCACCCCACT

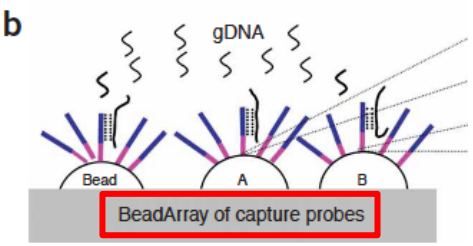
Illumina and/or PE Biosystems, deliberately redacted the actual “Tag Sequences” from the 2004 settlement agreement, to deprive the true inventors of rightful royalties. The recent FOIA request revealed “Tag sequences” be 24 to 26 + 2 bases in length (addition of an extra “T” to both the 3’ and 5’ end does not materially affect the performance characteristics of these sequences); Tag sequences differ from each other by 25% or more within those 24-26 bases, and are designed to operate under uniform hybridization conditions, in other words, they literally infringe upon the intellectual property of WO97/31256, i.e. the “Zip Code Chemistry” invented by the Barany Lab.

Illumina Plagiarizes the Zirvi-Barany Zip Codes

Zip-code Array, Zip, Decoder sequence, IllumaCode, IllumiCode, Probe sequence, BeadArray capture probes, Adapter Sequence,

TABLE 1

IllumaCode ID	Decoder (5'-3')
17	GGCTGGTTCGGCCCGAAAGCTTAG
18	GTTCCCAGTGAAGCTGCGATCTGG
19	TACTTGGCATGGAATCCCTTACGC
20	ACTAGCATATTTCAGGGCACCGGC

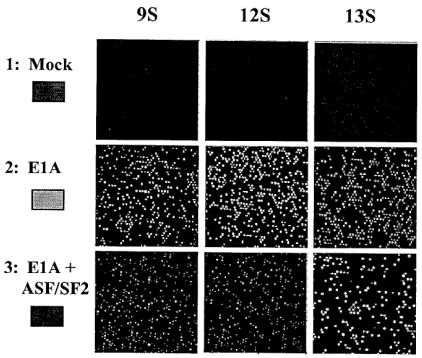


Detection of Alternative Splicing on Zip-Code Arrays and Comparison with RT-PCR

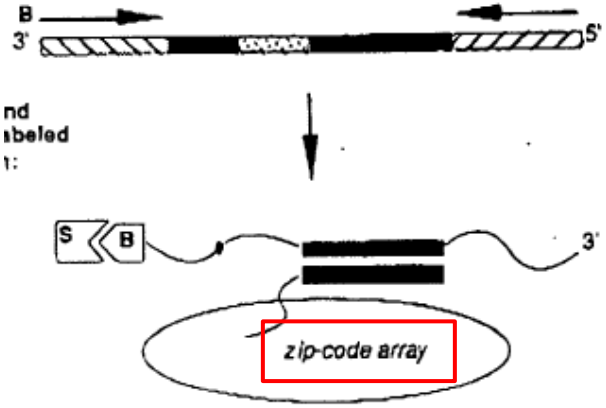
TABLE 2

IllumaCode ID	Decoder Sequence (5'-3')	Probe Sequence (5'-3')
1	TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTAGAAGCAGCGGCGAA
2	TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA
3	AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT
4	CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG
5	ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT
6	TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA
7	CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG
8	CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG
9	TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA
10	GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC
11	TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA
12	CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG
13	GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC
14	AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT
15	CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG
16	CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG
17	GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC
18	GTTCCCAGTGAAGCTGCGATCTGG	CCAGATCGCAGCTTCACTGGGAAC
19	TACTTGGCATGGAATCCCTTACGC	GCGTAAGGGATTCCATGCCAAGTA
20	ACTAGCATATTTCAGGGCACCGGC	GCCGGTGCCCTGAAATATGCTAGT

A. Array Images



5' to 3'; note the direction from right to left): an upstream universal 18 nt priming site (U), a unique 20 nt zip-code sequence (Zip) to target the oligo to a specific address on the array, a 20



In these Illumina patent applications, Illumina uses the terms "Zip-code Array", "Zip", "Decoder sequence", "IllumaCode", "Probe sequence", and "BeadArray capture probes" to describe Zirvi-Barany's (*exact*) 24-mer zip code sequences.

Zip code, cZip, Decoders, IllumaCode, IlluniCode, Capture Probe, Bead identifier, Target, Universal Tag Sequence

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Strategies for Covalent Attachment of DNA to Beads

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accepted 1 September 2003
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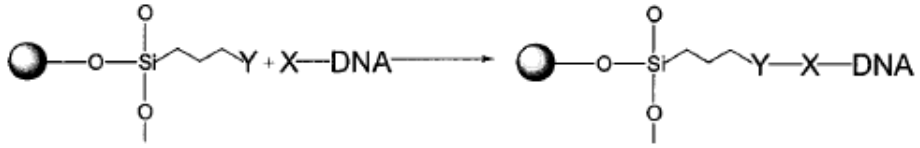


Y functional group
X 5' modification group

FIGURE 3 A general oligo immobilization scheme.

MATERIALS AND METHODS

Chemical Reagents

Silica beads in water (3 μm diameter, ~5×10^{10} beads/g) were obtained from Bangs Laboratories, Inc., Carmel, IN. Silanization reagents, 3-aminopropyltrimethoxysilane, 3-mercaptopropyltrimethoxysilane, and 3-glycidoxypropyltrimethoxysilane were obtained from United Chemical Technologies (UCT), Bristol, PA. Succinimidyl 4-hydrazinonicotinate acetone hydrazone, and 5′-aldehyde modified oligonucleotide 5′-(CHO) TTT GAA AAG CCT ACA CGA CGG CGA A-3′ (capture probe) were obtained from Solulink, San Diego, CA. All other oligonucleotides 5′-NH_2-TTT GAA AAG GGA CGT GCG CTT CGA A-3′ (capture probe), 5′-HS-TTT GAA AAG GGA CGT GCG CTT CGA A-3′ (capture probe), 5′-FAM-TTT CGC CGT CGT GTA GGC TTT TCA A-3′ (target), 5′-FAM-TTT CGA AGC GCA CGT CCC TTT TCA A-3′ (target), were obtained from Operon Technologies, Alameda, CA, or synthesized in house using the Oligator™ technology. All oligonucleotides were high performance liquid chromatography (HPLC) purified. All other reagents were obtained from NovaBiochem, Aldrich or Sigma. All solutions were prepared with OmniPur™ (sterile, nuclease free) water from Merck.

Complementary Oligonucleotide (Target) Hybridization. Hybridization of complementary oligo (target) to beads containing immobilized probes was carried out in solution and fluorescence-activated cell sorter (FACS) was used to measure hybridization intensity.

Hybridization was done in solution as follows: about 1 mg of probe-immobilized beads were suspended in 30 μL hybridization buffer (0.1*M* potassium phosphate, 1*M* sodium chloride, 0.1% Tween-20, and 5% ethanol, pH 7.6), followed by addition of 15–20 μL of ~1 m*M* target (in 0.05*M* borate buffer, pH 8.5) and then shaken for 2 h. The beads were washed 2–3 times with hybridization buffer to remove excess target oligonucleotides. For the release of target from the beads, the beads were incubated with 50 μL of 0.1*M* sodium hydroxide solution for 10 min.

In this Illumina publication describing chemistry for Infinium arrays, Illumina uses the terms “Capture Probe”, and “target” to describe Zirvi-Barany’s *exact* 24-mer zip code sequences (with an extra T on the 5’ end).

Zip code, cZip, Decoders, IllumaCode, IlluniCode, Capture Probe, Target, Address 1, Address 2, Universal Tag Sequence

Bioconjugate Chem. **2006**, *17*, 841–848 841

Synthetic Modification of Silica Beads That Allows for Sequential Attachment of Two Different Oligonucleotides

Gali Steinberg-Tatman, Michael Huynh, David Barker, and Chanfeng Zhao*

Illumina Inc., 9885 Towne Centre Drive, San Diego, California 92121. Received January 19, 2006; Revised Manuscript Received February 22, 2006

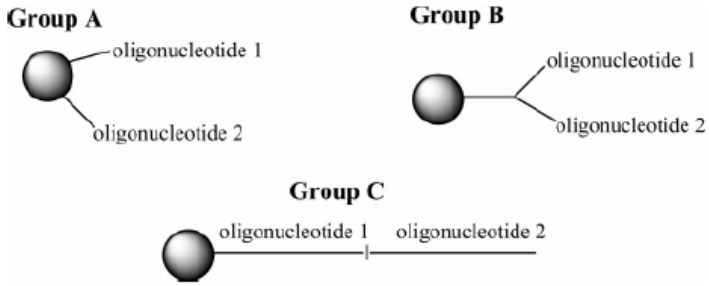


Figure 1. Potential schemes for two oligonucleotide attachment.

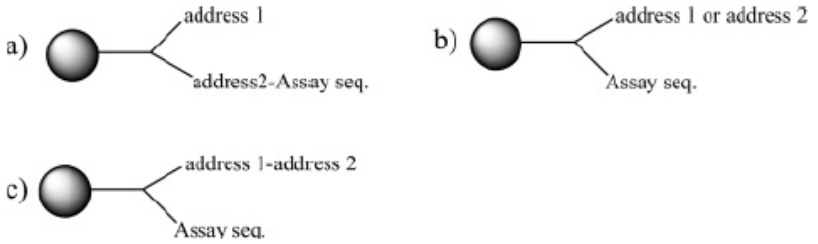


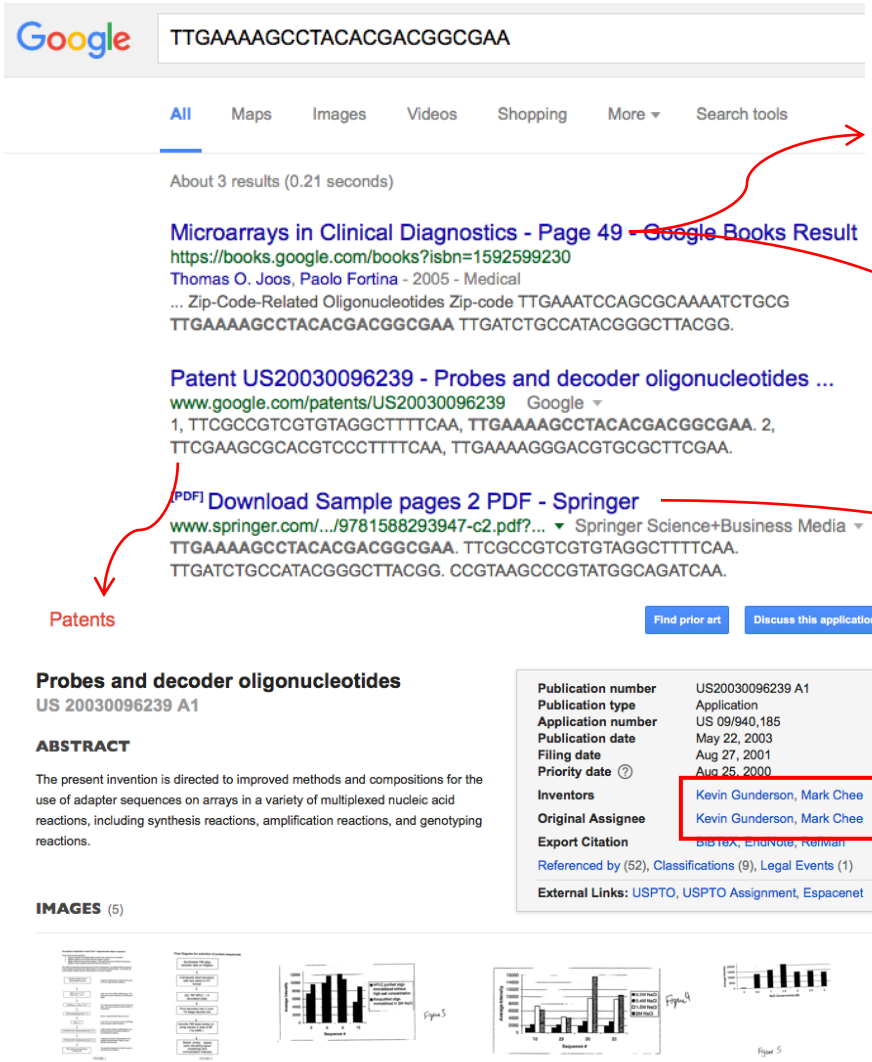
Figure 3. Detailed potential encoding schemes of group B from Figure 1.

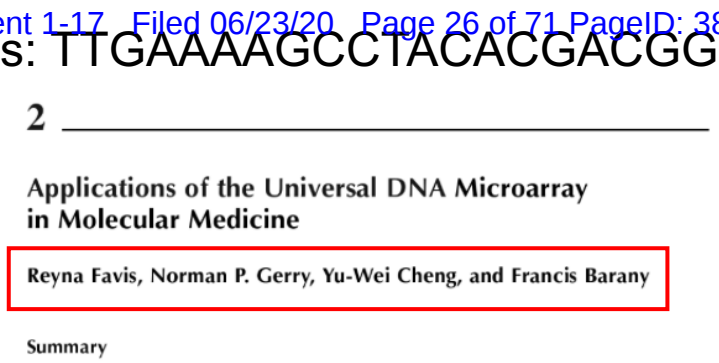
Table 1. Hybridization Intensities of First and Second Sequences Resulting from the Different Activation/Attachment Chemistries for the Second Sequence

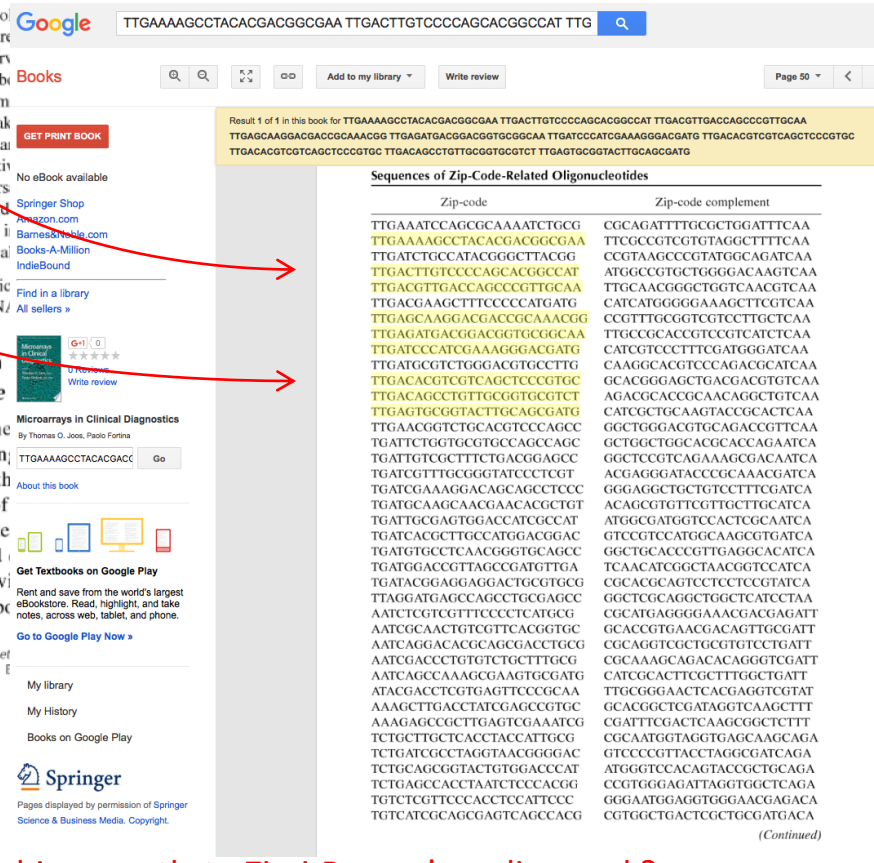
1st Sequence: S9 5′ (NH_2) TTTGATGTCCCATTCCCCACGCGTT					
2nd Sequence: S13 5′ (NH_2 or CHO) TTTGATCGTAGCCGGTATGCGACGG					
immobilization chemistries for 2nd attachment	5A	5B	5C	5D	5E
hybridization intensity of the 1st sequence before the 2nd sequence was immobilized	4978	5100	5154	5120	4978
hybridization intensity of 1st sequence after the 2nd sequence was immobilized	3925	2640	2729	2852	2670
hybridization intensity of the 2nd sequence	808	205	457	430	2950
1st Sequence: S13 5′ (NH_2) TTTGATCGTAGCCGGTATGCGACGG					
2nd Sequence: S9 5′ (NH_2 or CHO) TTTGATGTCCCATTCCCCACGCGTT					
immobilization chemistries for 2nd attachment	5A	5B	5C	5D	5E
hybridization intensity of the 1st sequence before the 2nd sequence was immobilized	3095	2872	2950	2930	3093
hybridization intensity of 1st sequence after the 2nd sequence was immobilized	2488	1500	1580	1550	1650
hybridization intensity of the 2nd sequence	1400	108	800	820	4800

In this Illumina publication describing chemistry for Infinium arrays, Illumina uses the terms “Capture Probe”, “target”, “Address 1” and “Address 2” to describe Zrivi-Barany’s *exact* 24-mer zip code sequences (with an extra T on the 5’ end).

A closer look at one of the 16 zip codes: TTGAAAAGCCTACACGACGGCGAA







Chances of 9 new "Illumacode" zip code sequences matching exactly to Zirvi-Barany's earlier work?
One in 10^{130} or a Googol (1×10^{100}) times the total number of stars in the Universe (1×10^{29})!

The 16 zip codes, plagiarized from Zirvi-Barany's unpublished document in the identical order:

The 16 zip codes in original unpublished 465 order

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	1	3	8	77.6	TTGAAATCCAGCGCAAAATCTGCG		1	4	31	21	4	29		CGCAGATTTTGCGCTGGATTTCAA		75.6
2	2	5	15	77.2	TTGAAAAGCCTACACGACGGCGAA		1	6	26	30	35	16		TTCGCCGTCGTGTAGGCTTTTCAA	1	77.3
3	97	6	18	79.1	TTGAAAAGGGACGTGCGCTTCGAA		1	6	34	33	17	16		TTCGAAGCCGCACGTCCCTTTTCAA	2	77.7
4	3	7	22	76.5	TTGATCTGCCATACGGGCTTACGG		1	8	15	35	17	35		CCGTAAGCCCGTATGGCAGATCAA		76.5
5	98	8	25	79.5	TTGATCTGCACGGTTGTGCGGTA		1	8	30	12	33	18		TACCGCACAACGCGTGCAGATCAA		79.1
6	99	9	29	80.3	TTGATGTCCCATTCCCCACGCGTT		1	9	15	28	30	12		AACGCGTGGGGAATGGGACATCAA	3	78.9
7	66	12	42	81.5	TTGATCGTGGACACGGCACGCTCA		1	10	34	35	30	13		TGAGCGTCCCGTGTCCACGATCAA		80.1
8	100	13	43	79.2	TTGATCGTAGCCGGTATGCGACGG		1	10	36	18	29	35		CCGTCGCATACCGGCTACGATCAA	4	77.8
9	4	15	45	80.6	TTGACTTGTCCCCAGCACGGCCAT		1	11	28	31	35	15		ATGGCCGTGCTGGGGACAAGTCAA	5	80.4
10	5	17	56	80.4	TTGACGTTGACCAGCCCGTTGCAA		1	12	32	36	12	21		TTGCAACGGGCTGGTCAACGTCAA	6	79.5
11	101	18	64	79.7	TTGACCATGCTTCGAAACGGCGAA		1	15	17	16	35	16		TTCGCCGTTTCGAAGCATGGTCAA		77.8
12	6	20	72	76.4	TTGACGAAGCTTTCCCCCATGATG		1	16	17	28	15	27		CATCATGGGGGAAAGCTTCGTCAA		75.6
13	102	21	75	77.4	TTGACGAAATCGGCAACCTATGCG		1	16	24	21	26	29		CGCATAGGTTGCCGATTTCGTCAA	7	76.0
14	7	24	90	81.2	TTGAGCAAGGACGACCGCAAACGG		1	21	34	32	21	35		CCGTTTGCGGTCGTCCTTGCTCAA	8	79.1
15	67	26	94	78.2	TTGAAGTGCAGCCACGAAAGCGAA		1	22	31	30	6	16		TTCGCTTTCGTGGCTGCACTTCAA	9	78.0
16	68	29	112	79.3	TTGAATCGGAGTTGCGCGTTGGAC		1	24	20	29	12	34		GTCCAACGCGCAACTCCGATTCAA	10	77.7
17	8	30	126	82.4	TTGAGATGACGGACGGTGCGGCAA		1	27	35	35	29	21		TTGCCGCACCGTCCGTCATCTCAA	11	80.2
18	103	32	12925	75.7	TTGATCCCGGTATTAGAGCCCACG		1	28	18	3	36	30		CGTGGGCTCTAATACCGGGATCAA		75.9
19	9	33	140	76.3	TTGATCCCATCGAAAGGGACGATG		1	28	24	6	34	27		CATCGTCCCTTTCGATGGGATCAA	12	74.9
20	10	36	150	80.1	TTGATCGCGTCTGGGACGTGCCTTG		1	29	8	34	33	11		CAAGGCACGTCCCAGACGCATCAA		78.8
21	104	42	161	80.7	TTGATGCGTGCGCTCAATCGAGGA		1	29	29	13	24	25		TCCTCGATTGAGCGCACGCATCAA		78.8
22	105	43	165	80.1	TTGATGCGAGCCGATGCCATCTTG		1	29	36	27	15	11		CAAGATGGCATCGGCTCGCATCAA		77.6
23	11	44	166	80.3	TTGACACGTCGTCAGCTCCCGTGC		1	30	10	31	28	33		GCACGGGAGCTGACGACGTGTCAA	13	79.9
24	12	48	180	80	TTGACAGCCTGTTGCGGTGCGTCT		1	31	14	29	33	19		AGACGCACCGCAACAGGCTGTCAA	14	80.6
25	106	49	186	79.1	TTGACAGCACGGGACCCCTACACG		1	31	35	32	26	30		CGTGTAGGGGTCCCGTGCTGTCAA	15	79.4
26	13	52	202	76.5	TTGAGTGCGGTACTTGCAGCGATG		1	33	18	11	31	27		CATCGCTGCAAGTACCGCACTCAA	16	77.3
27	107	53	208	80.3	TTGAGTGCTCCCGCAACGTTGTGC		1	33	28	21	12	33		GCACAACGTTGCGGGAGCACTCAA		79.6
28	14	55	222	81.2	TTGAACGGTCTGCACGTCCCAGCC		1	35	8	30	28	36		GGCTGGGACGTGCAGACCGTTCAA		80.2
29	108	58	230	76.8	TTGAACGGGCAAACCTCTTGCTTG		1	35	21	23	11	11		CAAGCAAGAGGTTTGCCCGTTCAA		76.6
30	109	59	232	78.7	TTGAACGGGATGGCAAGGACCTCA		1	35	27	21	34	13		TGAGGTCCTTGCCATCCCGTTCAA		78.3

9 of the 16 zip codes in final 4,633 patent order

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	1	3	8	77.6	TTGAAATCCAGCGCAAAATCTGCG		1	4	31	21	4	29		CGCAGATTTTGCGCTGGATTTCAA		75.6
2	2	5	15	77.2	TTGAAAAGCCTACACGACGGCGAA		1	6	26	30	35	16		TTCGCCGTCGTGTAGGCTTTTCAA	1	77.3
3	3	7	22	76.5	TTGATCTGCCATACGGGCTTACGG		1	8	15	35	17	35		CCGTAAGCCCGTATGGCAGATCAA		76.5
4	4	15	45	80.6	TTGACTTGTCCCCAGCACGGCCAT		1	11	28	31	35	15		ATGGCCGTGCTGGGGACAAGTCAA	5	80.4
5	5	17	56	80.4	TTGACGTTGACCAGCCCGTTGCAA		1	12	32	36	12	21		TTGCAACGGGCTGGTCAACGTCAA	6	79.5
6	6	20	72	76.4	TTGACGAAGCTTTCCCCCATGATG		1	16	17	28	15	27		CATCATGGGGGAAAGCTTCGTCAA		75.6
7	7	24	90	81.2	TTGAGCAAGGACGACCGCAAACGG		1	21	34	32	21	35		CCGTTTGCGGTCGTCCTTGCTCAA	8	79.1
8	8	30	126	82.4	TTGAGATGACGGACGGTGCGGCAA		1	27	35	35	29	21		TTGCCGCACCGTCCGTCATCTCAA	11	80.2
9	9	33	140	76.3	TTGATCCCATCGAAAGGGACGATG		1	28	24	6	34	27		CATCGTCCCTTTCGATGGGATCAA	12	74.9
10	10	36	150	80.1	TTGATGCGTCTGGGACGTGCCTTG		1	29	8	34	33	11		CAAGGCACGTCCCAGACGCATCAA		78.8
11	11	44	166	80.3	TTGACACGTCGTCAGCTCCCGTGC		1	30	10	31	28	33		GCACGGGAGCTGACGACGTGTCAA	13	79.9
12	12	48	180	80	TTGACAGCCTGTTGCGGTGCGTCT		1	31	14	29	33	19		AGACGCACCGCAACAGGCTGTCAA	14	80.6
13	13	52	202	76.5	TTGAGTGCGGTACTTGCAGCGATG		1	33	18	11	31	27		CATCGCTGCAAGTACCGCACTCAA	16	77.3
14	14	55	222	81.2	TTGAACGGTCTGCACGTCCCAGCC		1	35	8	30	28	36		GGCTGGGACGTGCAGACCGTTCAA		80.2
15	15	67	269	82.2	TGATTCTGGTGCGTGCCAGCCAGC		2	8	33	33	31	31		GCTGGCTGGCACGCACCAGAATCA		80.9
16	16	69	274	76.8	TGATTGTCGCTTTCTGACGGAGCC		2	9	17	8	35	36		GGCTCCGTCAGAAAGCGACAATCA		77.0
17	17	73	294	77.9	TGATCGTTTGCGGGTATCCCTCGT		2	12	29	18	28	10		ACGAGGGATACCCGCAAACGATCA		77.8
18	18	75	310	77.9	TGATCGAAAGGACAGCAGCCTCCC		2	16	25	31	36	28		GGGAGGCTGCTGTCCTTTCGATCA		78.0
19	19	79	328	76.9	TGATGCAAGCAACGAACACGCTGT		2	21	21	16	30	14		ACAGCGTGTTCGTTGCTTGCATCA		78.2
20	20	92	372	79.5	TGATTGCGAGTGGACCATCGCCAT		2	29	22	32	24	15		ATGGCGATGGTCCACTCGCAATCA		78.7
21	21	94	379	80	TGATCACGCTTGCCATGGACGGAC		2	30	11	15	34	34		GTCCGTCCATGGCAAGCGTGATCA		78.7
22	22	104	418	82	TGATGTGCCTCAACGGGTGCAGCC		2	33	13	35	33	36		GGCTGCACCCGTTGAGGCACATCA		80.7
23	23	111	431	75.6	TGATGGACCGTTAGCCGATGTTGA		2	34	12	36	27	1		TCAACATCGGCTAACGGTCCATCA		76.4
24	24	118	444	79.5	TGATACGGAGGAGGACTGCGTGCG		2	35	25	34	29	29		CGCACGCAGTCCTCCTCCGTATCA		79.0
25	25	129	555	79.9	TTAGGATGAGCCAGCCTGCGAGCC		3	27	36	36	29	36		GGCTCGCAGGCTGGCTCATCCTAA		79.7
26	26	151	690	77.7	AATCTCGTCGTTTCCCCTCATGCG		4	10	12	28	13	29		CGCATGAGGGGAAACGACGAGATT		76.8
27	27	166	805	77.4	AATCGCAACTGTCGTTCACGGTGC		4	21	14	12	30	33		GCACCGTGAACGACAGTTGCGATT		77.9
28	28	167	842	81.4	AATCAGGACACGCAGCGACCTGCG		4	25	30	31	32	29		CGCAGGTCGCTGCGTGTCCTGATT		80.3
29	29	183	926	76.7	AATCGACCCTGTGTCTGCTTTGCG		4	32	14	19	17	29		CGCAAAGCAGACACAGGGTCGATT		77.4
30	30	197	983	76.9	AATCAGCCAAAGCGAAGTGCGATG		4	36	6	16	33	27		CATCGCACTTCGCTTTGGCTGATT		76.6

The 16 zip codes listed in Illumina's US20030096239 are in the same order as the original unpublished 465

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
1	1		TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA	77.3	1		5	15	77.2	TTGAAAAGCCTACACGACGGCGAA		1	6	26	30	35	16		TTCGCCGTCGTGTAGGCTTTTCAA
2	2		TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA	77.7	2		6	18	79.1	TTGAAAAGGGACGTGCGCTTCGAA		1	6	34	33	17	16		TTCGAAGCGCACGTCCCTTTTCAA
3	3		AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT	78.9	3		9	29	80.3	TTGATGTCCCATTCCCCACGCGTT		1	9	15	28	30	12		AACGCGTGGGGAATGGGACATCAA
4	4		CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG	77.8	4		13	43	79.2	TTGATCGTAGCCGGTATGCGACGG		1	10	36	18	29	35		CCGTCGCATACCGGCTACGATCAA
5	5		ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT	80.4	5		15	45	80.6	TTGACTTGTCCCCAGCACGGCCAT		1	11	28	31	35	15		ATGGCCGTGCTGGGGACAAGTCAA
6	6		TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA	79.5	6		17	56	80.4	TTGACGTTGACCAGCCCGTTGCAA		1	12	32	36	12	21		TTGCAACGGGCTGGTCAACGTCAA
7	7		CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG	76.0	7		21	75	77.4	TTGACGAAATCGGCAACCTATGCG		1	16	24	21	26	29		CGCATAGGTTGCCGATTTCGTCAA
8	8		CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG	79.1	8		24	90	81.2	TTGAGCAAGGACGACCGCAAACGG		1	21	34	32	21	35		CCGTTTGCGGTCGTCCTTGCTCAA
9	9		TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA	78.0	9		26	94	78.2	TTGAAGTGCAGCCACGAAAGCGAA		1	22	31	30	6	16		TTCGCTTTCGTGGCTGCACTTCAA
10	10		GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC	77.7	10		29	112	79.3	TTGAATCGGAGTTGCGCGTTGGAC		1	24	20	29	12	34		GTCCAACGCGCAACTCCGATTCAA
11	11		TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA	80.2	11		30	126	82.4	TTGAGATGACGGACGGTGCGGCAA		1	27	35	35	29	21		TTGCCGCACCGTCCGTCATCTCAA
12	12		CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG	74.9	12		33	140	76.3	TTGATCCCATCGAAAGGGACGATG		1	28	24	6	34	27		CATCGTCCCTTTCGATGGGATCAA
13	13		GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC	79.9	13		44	166	80.3	TTGACACGTCGTCAGCTCCCGTGC		1	30	10	31	28	33		GCACGGGAGCTGACGACGTGTCAA
14	14		AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT	80.6	14		48	180	80	TTGACAGCCTGTTGCGGTGCGTCT		1	31	14	29	33	19		AGACGCACCGCAACAGGCTGTCAA
15	15		CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG	79.4	15		49	186	79.1	TTGACAGCACGGGACCCCTACACG		1	31	35	32	26	30		CGTGTAGGGGTCCCGTGCTGTCAA
16	16		CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG	77.3	16		52	202	76.5	TTGAGTGCGGTACTTGCAGCGATG		1	33	18	11	31	27		CATCGCTGCAAGTACCGCACTCAA
17	17		GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC	78.8															
18	18		GTTCCCAGTGAAGCTGCGATCTGG	CCAGATCGCAGCTTCACTGGGAAC	76.9															
19	19		TACTTGGCATGGAATCCCTTACGC	GCGTAAGGGATTCCATGCCAAGTA	75.2															
20	20		ACTAGCATATTTCAGGGCACCGGC	GCCGGTGCCCTGAAATATGCTAGT	76.9						Tm values calculated for first 110 zip-codes using OligoAnalyzer 3.1 program									
21	21		GAACGGTCAATGAACCCGCTGTGA	TCACAGCGGGTTCATTGACCGTTC	77.2						under standard hybridization conditions									
22	22		GCGGCCTTGGTTCAATATGAATCG	CGATTCATATTGAACCAAGGCCGC	74.6															
23	23		GATCGTTAGAGGGACCTTGCCCGA	TCGGGCAAGGTCCCTCTAACGATC	77.2						Oligo Concentration:	0.25 uM								
24	24		TGGACCTAGTCCGGCAGTGACGAA	TTCGTCACTGCCGGACTAGGTCCA	78.7						Na+ Concentration:	1000 mM								
25	25		ATAAACTACCCAGGACGGGCGGAA	TTCCGCCCGTCCTGGGTAGTTTAT	77.6						Mg++ Concentration:	0 mM								

Chances of first 4 bases of 16 zip code sequences matching TTGA, which is our first tetramer?

One in 3 x 10^{38} or more than a billion times the total number of stars in the Universe! (1 x 10^{29})

An unexplained coincidence?

Barany *et al.*, filed, April 14, 2000

(12) **United States Patent**
Barany et al.

(10) **Patent No.: US 7,455,965 B2**
(45) **Date of Patent: Nov. 25, 2008**

(54) **METHOD OF DESIGNING ADDRESSABLE ARRAY FOR DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING LIGASE DETECTION REACTION**

(75) Inventors: **Francis Barany**, New York, NY (US); **Monib Zirvi**, Willingboro, NJ (US); **Norman P. Gerry**, Boston, MA (US); **Reyna Favis**, Iselin, NJ (US); **Richard Kliman**, Iselin, NJ (US)

FOREIGN PATENT DOCUMENTS

EP 0 357 011 8/1989

(Continued)

OTHER PUBLICATIONS

"Nucleic Acid Hybridization—General Aspects," in *Nonradioactive In Situ Hybridization Application Manual*, Indianapolis, Indiana:

Illumina, filed Aug. 25, 2000 – Never Issues

(19) **United States**
(12) **Patent Application Publication**
Gunderson et al.

(10) **Pub. No.: US 2003/0096239 A1**
(43) **Pub. Date: May 22, 2003**

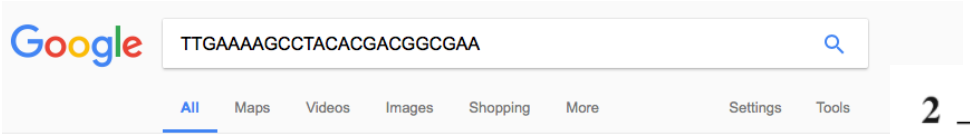
(54) **PROBES AND DECODER OLIGONUCLEOTIDES**

(76) Inventors: **Kevin Gunderson**, Encinitas, CA (US); **Mark Chee**, Del Mar, CA (US)

Related U.S. Application Data

(60) Provisional application No. 60/227,948, filed on Aug. 25, 2000. Provisional application No. 60/228,854, filed on Aug. 29, 2000.

Google search of: TTGAAAAGCCTACACGACGGCGAA



About 5 results (0.45 seconds)

Probes and decoder oligonucleotides
US 20030096239 A1

ABSTRACT

The present invention is directed to improved methods and compositions for the use of adapter sequences on arrays in a variety of multiplexed nucleic acid reactions, including synthesis reactions, amplification reactions, and genotyping reactions.

[PDF] Download Sample pages 2 PDF - Springer
www.springer.com/cda/content/document/cda.../97815882939 47-c2.pdf?SGWID... ▾
TTGAAAAGCCTACACGACGGCGAA. TTCGCCGTCGTGTAGGCTTTTCAA.
TTGATCTGCCATACGGGCTTACGG. CCGTAAGCCCGTATGGCAGATCAA.

US20030096239 - Google
www.google.com/patents/US20030096239
1, TTCGCCGTCGTGTAGGCTTTTCAA, **TTGAAAAGCCTACACGACGGCGAA**. 2,
TTCGAAGCGCACGTCCCTTTTCAA, TTGAAAAGGGACGTGCGCTTCGAA.

Publication number	US20030096239 A1
Publication type	Application
Application number	US 09/940,185
Publication date	May 22, 2003
Filing date	Aug 27, 2001
Priority date	Aug 25, 2000
Inventors	Kevin Gunderson, Mark Chee
Original Assignee	Kevin Gunderson, Mark Chee
Export Citation	BiBTeX, EndNote, RefMan

Referenced by (52), Classifications (9), Legal Events (1)

External Links: USPTO, USPTO Assignment, Espacenet

Notes - Protein Microarrays - ALPF Medical Research
www.alpfmedical.info › Protein Microarrays
We recommend the software program Oligo for LDR primer design. This program is also useful in designing PCR and multiplex PCR primers. This program ...

Microarrays in Clinical Diagnostics - Page 49 - Google Books Result
https://books.google.com/books?isbn=1592599230
Thomas O. Joos, Paolo Fortina - 2005 - Medical
... Zip-Code-Related Oligonucleotides Zip-code TTGAAATCCAGCGCAAAATCTGCG
TTGAAAAGCCTACACGACGGCGAA TTGATCTGCCATACGGGCTTACGG.

Full text of "USPTO Patents Application 09940185" - Internet Archive
https://archive.org/stream/gov.uspto.../09940185-2002-01-31-00002-A.PE_djvu.txt ▾
... **TTGAAAAGCCTACACGACGGCGAA** 2 TTCGAAGCGCACGTCCCTTTTCAA
TTGAAAAGGGACGTGCGCTTCGAA 3 AACGCGTGGGGAATGGGACATCAA TTG ...

Full text of "USPTO Patents Application 09940185" - Internet Archive
https://archive.org/stream/gov.uspto.../09940185-2001-08-27-00001-LET._djvu.txt ▾
... 1 1 OOOOO 1 OO 1 O 1 AAOOO 1 1 1 1 **TTGAAAAGCCTACACGACGGCGAA** 9 Z.
TTPGAAGPGPAPGTPPPTTTTOAA TTGAAAAGGGACGTGCGCTTCGAA i i ...

Seq. ID No.

Decoder Sequence (5'-3')

Probe Sequence (5-3')

1

TTCGCCGTCGTGTAGGCTTTTCAA

TTGAAAAGCCTACACGACGGCGAA

USPTO archives of all the Illumina filings and patent office correspondence may now be found relating to the plagiarized Zirvi-Barany zip codes

2

Applications of the Universal DNA Microarray in Molecular Medicine

Reyna Favis, Norman P. Gerry, Yu-Wei Cheng, and Francis Barany

Summary

Integration of molecular medicine into standard clinical practice will require the availability of diagnostics that are sensitive, rapid, and robust. The backbone technology underlying the diagnostic will likely serve double duty during clinical trials in order to first validate the biomarkers that contribute to both drug response and disease stratification. PCR/LDR/Universal DNA microarray is a promising technology to help drive the transition from the current paradigms of clinical decision making to the new era of personalized medicine. By uncoupling the mutation detection step from array hybridization, this technology becomes fully programmable. It exploits full use of the sensitivity that the ligase detection reaction can provide, while maintaining a rapid read out on a universal microarray. Thus, PCR/LDR/Universal DNA microarray is 50-fold more sensitive and 10-fold more rapid than conventional hybridization-only arrays. The intent of this

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Table 1
Sequences of Zip-Code-Related Oligonucleotides

Zip-code	Zip-code complement
TTGAAATCCAGCGCAAAATCTGCG	CGCAGATTTTGCGCTGGATTTCAA
TTGAAAAGCCTACACGACGGCGAA	TTCGCCGTCGTGTAGGCTTTTCAA
TTGATCTGCCATACGGGCTTACGG	CCGTAAGCCCGTATGGCAGATCAA
TTGACTTGTCCCCAGCACGGCCAT	ATGGCCGTGCTGGGGACAAGTCAA
TTGACGTTGACCAGCCCGTTGCAA	TTGCAACGGGCTGGTCAACGTCAA
TTGACGAAGCTTTCCCCCATGATG	CATCATGGGGGAAAGCTTCGTCAA
TTGAGCAAGGACGACCGCAAACGG	CCGTTTGCGGTCGTCCTTGCTCAA
TTGAGATGACGGACGGTGCGGCAA	TTGCCGCACCGTCCGTCATCTCAA
TTGATCCCATCGAAAGGGACGATG	CATCGTCCCTTTCGATGGGATCAA
TTGATGCGTCTGGGACGTGCCTTG	CAAGGCACGTCCCAGACGCATCAA
TTGACACGTCGTCAGCTCCCGTGC	GCACGGGAGCTGACGACGTGTCAA
TTGACAGCCTGTTGCGGTGCGTCT	AGACGCACCGCAACAGGCTGTCAA
TTGAGTGCGGTACTTGCAGCGATG	CATCGCTGCAAGTACCGCACTCAA
TTGAACGGTCTGCACGTCCCAGCC	GGCTGGGACGTGCAGACCGTTCAA

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Illumina tries to re-patent Zirvi-Barany's zip code sequences, renames them "IllumaCode ID", and later "Seq. ID No.".

Barany *et al.*, filed, April 14, 2000

(12) **United States Patent**
Barany et al.

(10) **Patent No.: US 7,455,965 B2**
(45) **Date of Patent: Nov. 25, 2008**

(54) **METHOD OF DESIGNING ADDRESSABLE ARRAY FOR DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING LIGASE DETECTION REACTION**

(75) Inventors: **Francis Barany**, New York, NY (US); **Monib Zirvi**, Willingboro, NJ (US); **Norman P. Gerry**, Boston, MA (US); **Reyna Favis**, Iselin, NJ (US); **Richard Kliman**, Iselin, NJ (US)

FOREIGN PATENT DOCUMENTS

EP 0 357 011 8/1989

(Continued)

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Illumina, filed Aug. 25, 2000 – Never Issues

(19) **United States**
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(76) Inventors: **Kevin Gunderson**, Encinitas, CA (US); **Mark Chee**, Del Mar, CA (US)

Related U.S. Application Data

(60) Provisional application No. 60/227,948, filed on Aug. 25, 2000. Provisional application No. 60/228,854, filed on Aug. 29, 2000.

SEQ ID NO:	4,633 ID#	HEX ID#	Tm	ZIPCODE (5'-3')	TETRAMER NUMBERS
1	3	8	77.6	TTGAAAATCCAGCGCAAAATCTGCG	1 4 31 21 4 29
2	5	15	77.2	TTGAAAAGCCTACACGACGGCGAA	1 6 26 30 35 16
3	7	22	76.5	TTGATCTGCCATACGGGCTTACGG	1 8 15 35 17 35
4	15	45	80.6	TTGACTTGTCCCCAGCACGGCCAT	1 11 28 31 35 15
5	17	56	80.4	TTGACGTTGACCAGCCCGTTGCAA	1 12 32 36 12 21
6	20	72	76.4	TTGACGAAGCTTTCCCCCATGATG	1 16 17 28 15 27
7	24	90	81.2	TTGAGCAAGGACGACCGCAAACGG	1 21 34 32 21 35
8	30	126	82.4	TTGAGATGACGGACGGTGCGGCAA	1 27 35 35 29 21
9	33	140	76.3	TTGATCCCATCGAAAGGGACGATG	1 28 24 6 34 27
10	36	150	80.1	TTGATGCGTCTGGGACGTGCCTTG	1 29 8 34 33 11
11	44	166	80.3	TTGACACGTCGTCAGCTCCCGTGC	1 30 10 31 28 33
12	48	180	80	TTGACAGCCTGTTGCGGTGCGTCT	1 31 14 29 33 19
13	52	202	76.5	TTGAGTGCGGTACTTGCAGCGATG	1 33 18 11 31 27
14	55	222	81.2	TTGAACGGTCTGCACGTCCCAGCC	1 35 8 30 28 36
15	67	269	82.2	TGATTCTGGTGCGTGCCAGCCAGC	2 8 33 33 31 31
16	69	274	76.8	TGATTGTCGCTTTCTGACGGAGCC	2 9 17 8 35 36

TABLE 2

IllumaCode ID	Decoder Sequence (5'-3')	Probe Sequence (5'-3')
1	TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA
2	TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA
3	AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT
4	CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG
5	ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT
6	TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA
7	CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG
8	CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG
9	TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA
10	GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC
11	TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA
12	CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG
13	GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC
14	AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT
15	CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG
16	CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG
17	GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC
18	GTTCCCAGTGAAGCTGCGATCTGG	CCAGATCGCAGCTTCACTGGGAAC
19	TACTTGGCATGGAATCCCTTACGC	GCGTAAGGGATTCCATGCCAAGTA
20	ACTAGCATATTTCAGGGCACCGGC	GCCGGTGCCCTGAAATATGCTAGT

Illumina – enabled by PE Biosystems providing them Zirvi-Barany's unpublished trade secret sequences sometime in 1999-2000 – attempted to re-patent Zirvi-Barany's ***exact*** zip code sequences. This is part of a deliberate strategy by Illumina and PE Biosystems – as evidenced by the un-redacted "First amendment to the Joint development agreement" to systematically and fraudulently purloin the true inventors intellectual property.

Gunderson & Chee plagiarized Zirvi-Barany's zip codes, which were used to achieve Illumina bead decoding.

1		TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA	77.3	1		5	15	77.2	TTGAAAAGCCTACACGACGGCGAA	1	6	26	30	35	16	TTCGCCGTCGTGTAGGCTTTTCAA
2		TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA	77.7	2		6	18	79.1	TTGAAAAGGGACGTGCGCTTCGAA	1	6	34	33	17	16	TTCGAAGCGCACGTCCCTTTTCAA
3		AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT	78.9	3		9	29	80.3	TTGATGTCCCATTCCCCACGCGTT	1	9	15	28	30	12	AACGCGTGGGGAATGGGACATCAA
4		CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG	77.8	4		13	43	79.2	TTGATCGTAGCCGGTATGCGACGG	1	10	36	18	29	35	CCGTCGCATACCGGCTACGATCAA
5		ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT	80.4	5		15	45	80.6	TTGACTTGTCCCCAGCACGGCCAT	1	11	28	31	35	15	ATGGCCGTGCTGGGGACAAGTCAA
6		TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA	79.5	6		17	56	80.4	TTGACGTTGACCAGCCCGTTGCAA	1	12	32	36	12	21	TTGCAACGGGCTGGTCAACGTCAA
7		CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG	76.0	7		21	75	77.4	TTGACGAAATCGGCAACCTATGCG	1	16	24	21	26	29	CGCATAGGTTGCCGATTTCGTCAA
8		CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG	79.1	8		24	90	81.2	TTGAGCAAGGACGACCGCAAACGG	1	21	34	32	21	35	CCGTTTGCGGTCGTCCTTGCTCAA
9		TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA	78.0	9		26	94	78.2	TTGAAGTGCAGCCACGAAAGCGAA	1	22	31	30	6	16	TTCGCTTTCGTGGCTGCACTTCAA
10		GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC	77.7	10		29	112	79.3	TTGAATCGGAGTTGCGCGTTGGAC	1	24	20	29	12	34	GTCCAACGCGCAACTCCGATTCAA
11		TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA	80.2	11		30	126	82.4	TTGAGATGACGGACGGTGCGGCAA	1	27	35	35	29	21	TTGCCGCACCGTCCGTCATCTCAA
12		CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG	74.9	12		33	140	76.3	TTGATCCCATCGAAAGGGACGATG	1	28	24	6	34	27	CATCGTCCCTTTCGATGGGATCAA
13		GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC	79.9	13		44	166	80.3	TTGACACGTCGTCAGCTCCCGTGC	1	30	10	31	28	33	GCACGGGAGCTGACGACGTGTCAA
14		AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT	80.6	14		48	180	80	TTGACAGCCTGTTGCGGTGCGTCT	1	31	14	29	33	19	AGACGCACCGCAACAGGCTGTCAA
15		CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG	79.4	15		49	186	79.1	TTGACAGCACGGGACCCCTACACG	1	31	35	32	26	30	CGTGTAGGGGTCCCGTGCTGTCAA
16		CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG	77.3	16		52	202	76.5	TTGAGTGCGGTACTTGCAGCGATG	1	33	18	11	31	27	CATCGCTGCAAGTACCGCACTCAA
17	17	GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC	78.8																
18	18	GTTCCCAGTGAAGCTGCGATCTGG	CCAGATCGCAGCTTCACTGGGAAC	76.9																
19	19	TACTTGGCATGGAATCCCTTACGC	GCGTAAGGGATTCCATGCCAAGTA	75.2																
20	20	ACTAGCATATTTCAGGGCACCGGC	GCCGGTGCCCTGAAATATGCTAGT	76.9						Tm values calculated for first 110 zip-codes using OligoAnalyzer 3.1 program										
21	21	GAACGGTCAATGAACCCGCTGTGA	TCACAGCGGGTTCATTGACCGTTC	77.2						under standard hybridization conditions										
22	22	GCGGCCTTGGTTCAATATGAATCG	CGATTCATATTGAACCAAGGCCGC	74.6																
23	23	GATCGTTAGAGGGACCTTGCCCGA	TCGGGCAAGGTCCCTCTAACGATC	77.2						Oligo Concentration:	0.25 uM									
24	24	TGGACCTAGTCCGGCAGTGACGAA	TTCGTCACTGCCGGACTAGGTCCA	78.7						Na+ Concentration:	1000 mM									
25	25	ATAAACTACCCAGGACGGGCGGAA	TTCCGCCCGTCCTGGGTAGTTTAT	77.6						Mg++ Concentration:	0 mM									
26	26	CATCGGTTCGCGCCAATCCAGATA	TATCTGGATTGGCGCGAACCGATG	76.9																
27	27	GTCGGGCATAGAGCCGACCACCCT	AGGGTGGTCGGCTCTATGCCCGAC	80.6																
28	28	CTTGGGTCATGATTCACCGTGCTA	TAGCACGGTGAATCATGACCCAAG	75.1																
29	29	TGCCTAACGTGCTAATCAGCAGCG	CGCTGCTGATTAGCACGTTAGGCA	77.2																
30	30	CGCATGTTGGAGCATATGCCCTGA	TCAGGGCATATGCTCCAACATGCG	77.3																
31	31	AGCCACTGCATCAGTGCTGTTCAA	TTGAACAGCACTGATGCAGTGGCT	77.6																
32	32	GGTTGTTTTGAGGCGTCCCACACT	AGTGTGGGACGCCTCAAAACAACC	77.5																
33	33	TCGACCAAGAGCAAGGGCGGACCA	TGGTCCGCCCTTGCTCTTGGTCGA	81.2																
34	34	GACATCGCTATTGCGCATGGATCA	TGATCCATGCGCAATAGCGATGTC	75.8																
35	35	GAAATACGAAGTCTGCGGGAGTCG	CGACTCCCGCAGACTTCGTATTTC	74.8																
36	36	TGTCATGAATGATTGATCGCGCGA	TCGCGCGATCAATCATTCATGACA	75.8																
37	37	ATATCGGGATTCGTTCCCGGTGAA	TTCACCGGGAACGAATCCCGATAT	76.1																
38	38	GCGAGCGTACCGAAGGGCCTAGAA	TTCTAGGCCCTTCGGTACGCTCGC	79.1																
39	39	TTACCGGCAGCGGACTTCCGAATT	AATTCGGAAGTCCGCTGCCGGTAA	78.5																
40	40	GTAATCGAGAGCTGCGCGCGGTCT	AGACGGCGCGCAGCTCTCGATTAC	79.7																
41	41	CCTGTTAGCGTAGGCGAGTCGATC	GATCGACTCGCGTACGCTAACAGG	76.0																
42	42	TAGCGGACCGGCAGAATGAGTTCC	GGAACTCATTCTGCCGGTCCGCTA	77.8																
43	43	GGTACATGCACTACGCGCACTCGG	CCGAGTGCGCGTAGTGCATGTACC	78.4																
44	44	AATTCATCTCGGACTCCCGCGGTA	TACCGCGGGAGTCCGAGATGAATT	77.4																
45	45	GCCAAATCTGGATTGGCAGGAATG	CATTCCTGCCAATCCAGATTTGGC	74.9																

Illumina – enabled by PE Biosystems providing them Zirvi-Barany's unpublished trade secret sequences sometime in 1999-2000 – attempted to re-patent Zirvi-Barany's ***exact*** zip code sequences. This is part of a deliberate strategy by Illumina and PE Biosystems – as evidenced by the un-redacted "First amendment to the Joint development agreement" to systematically and fraudulently purloin the true inventors intellectual property.

Zirvi-Barany describe properties of zip code addresses;
Illumina plagiarizes:

Zip code length of 24-mer.
"IllumaCodes" 24-mer Illumina Adapter sequences, "randomly picked by computer". In actuality, they seeded the program with 16 Zirvi-Barany zip codes.

Zirvi-Barany describe uniform hybridization. >85% of Tm values within the range of 75 – 80 C inclusive.
Illumina claims random 24-mers with Tm centered around 72° C and with a spread of 5 degrees which would be 67-77° C. In actuality, "IllumaCode" sequences also had Tm range of mostly 75-80° C inclusive, and almost all were 74-81° C, which is centered on the exact range as the Zirvi-Barany zip codes.

Barany Lab describe 25% or greater differences between two zip codes. For 24-mers, that equals probe-decoder complementarity score <= 18.
Illumina claims "Probe-Decoder complementarity Score < 14". In actuality; there are:
1,461 pairs with complementarity score of 14;
338 pairs with complementarity score of 15;
70 pairs with complementarity score of 16;
22 pairs with complementarity score of 17; and
1 pair with complementarity score of 18;
In other words 18/24 = 25% or greater differences - exactly matches Barany Lab teaching.

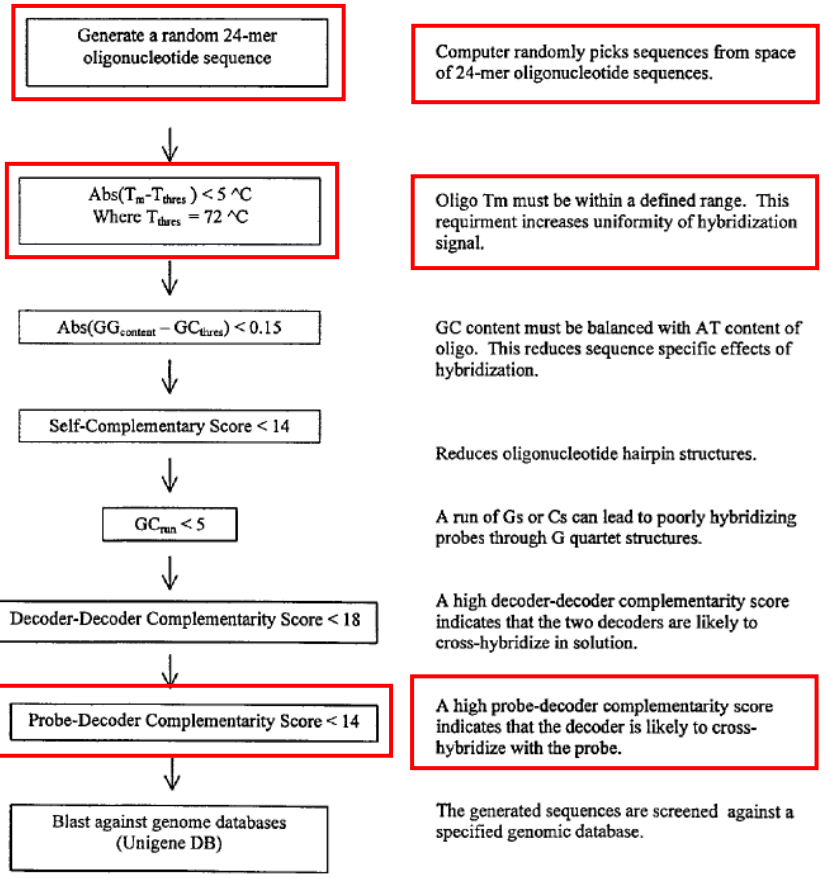
Illumina Application: Gunderson & Chee, Fig. 1

Description of algorithm to select "best" oligonucleotide adapter sequences.

Requirements for good sequences:

- Generates adequate hybridization signal intensity when employed in an experiment.
- Exhibits minimal cross-reactivity with other adapter sequences.
- Unique within the human genome sequence. This requirement can be extended to the genomic sequence of other organisms such as the fruit fly, the mouse, etc.

One method of generating sequences that meet the above requirements is to randomly generate sequences of given lengths and than pass these filters through a set of heuristic acceptance filters. In particular, the 24-mer Illumina Adapter sequences (IllumaCodes) were chosen as follows.



Illumina submits full application 09/940,185 on August 27, 2001:

Attorney Docket No.: A-69605-1/RMS/DCF [469249-00110]

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As the below named inventor, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name;

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROBES AND DECODER OLIGONUCLEOTIDES

the specification of which:
- ☐ is attached hereto.
- ☒ was filed on: August 27, 2001
  as Application No.: 09/940,185
  and was amended on: _____ (if applicable).

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56.

Illumina provides **false statements** to the USPTO, claiming to have invented "**Probes and decoder oligonucleotides**" when in fact they plagiarized the first 16 zipcodes directly from an unpublished Zirvi-Barany document they obtained through Illumina's collaboration with PE-Biosystems. They did this to avoid paying the true inventors their rightful royalties.

Attorney Docket No.: A-69605-1/RMS/DCF [469249-00110]

Signature: Kevin Gunderson Date 2/4/2003

Full Name of First Inventor: GUNDERSON (Family Name) Kevin (First Given Name) L. (Second Given Name)

Citizenship: United States of America

Residence: 1543 Juniper Hill Drive
Encinitas, California 92024

Post Office Address: Same as above

Signature: Mark Chee Date 2/4/2003

Full Name of Second Inventor: CHEE (Family Name) Mark (First Given Name) S. (Second Given Name)

Citizenship: Australia

Residence: 155 15th Street, No. 22
Del Mar, California 92014

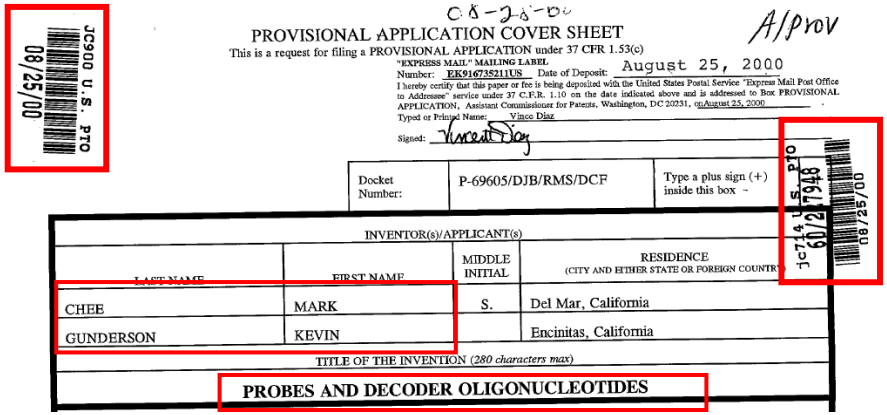
Post Office Address: Same as above

Kevin Gunderson and Mark Chee sign their name on February 4, 2003 to declare:

"I believe that I am the original, first, and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: **Probes and decoder oligonucleotides**."

"I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56."

Illumina submits provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000:



PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number: EK916735211US Date of Deposit: August 25, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box PROVISIONAL APPLICATION, Assistant Commissioner for Patents, Washington, DC 20231, on August 25, 2000

Typed or Printed Name: Vince Diaz

Signed:

Docket Number:	P-69605/DJB/RMS/DCF	Type a plus sign (+) inside this box →

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
CHEE	MARK	S.	Del Mar, California
GUNDERSON	KEVIN		Encinitas, California

TITLE OF THE INVENTION (280 characters max)

PROBES AND DECODER OLIGONUCLEOTIDES

TABLE 1

IllumaCode ID	Decoder (5'-3')
17	GGCTGGTTCGGCCCGAAAGCTTAG
18	GTTCCCAGTGAAGCTGCGATCTGG
19	TACTTGGCATGGAATCCCTTACGC
20	ACTAGCATATTTCAGGGCACCGGC

TABLE 2

IllumaCode ID	Decoder Sequence (5'-3')	Probe Sequence (5'-3')
1	TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA
2	TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA
3	AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT
4	CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG
5	ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT
6	TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA
7	CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG
8	CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG
9	TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA
10	GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC
11	TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA
12	CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG
13	GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC
14	AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT
15	CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG
16	CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG
17	GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC
18	GTTCCCAGTGAAGCTGCGATCTGG	CCAGATCGCAGCTTCACTGGGAAC
19	TACTTGGCATGGAATCCCTTACGC	GCGTAAGGGATTCCATGCCAAGTA
20	ACTAGCATATTTCAGGGCACCGGC	GCCGGTGCCCTGAAATATGCTAGT

TABLE 3

IllumaCode ID	Decoder Sequence (5'-3')	Probe Sequence (5'-3')
17	TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA
18	GTTCCCAGTGAAGCTGCGATCTGG	CCAGATCGCAGCTTCACTGGGAAC
19	TACTTGGCATGGAATCCCTTACGC	GCGTAAGGGATTCCATGCCAAGTA
20	ACTAGCATATTTCAGGGCACCGGC	GCCGGTGCCCTGAAATATGCTAGT
301	CCCGATATTCGCCCGGCCTATTCG	CGAATAGGCCGGGCGAATATCGGG
302	CGAGAAGATGCCTCACGCAACCAA	TTGGTTGCGTGAGGCATCTTCTCG
303	AACCTTGACCCGTGGATGACGCTA	TAGCGTCATCCACGGGTCAAGGTT
6	TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA
7	CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG
306	GCTTCCGGATGAACGGGATGGTTG	CAACCATCCCGTTCATCCGGAAGC
307	CCCTCCATGTTCTTCGAACGGTTT	AAACCGTTCGAAGAACATGGAGGG
308	TTGATGGGCGGCAATGCTCTTGCT	AGCAAGAGCATTGCCGCCCATCAA

TABLE 4

IllumaCode ID	Decoder Sequence (5'-3') + 5' T	Probe Sequence (5'-3') + 5' T
17	TTTCGCCGTCGTGTAGGCTTTTCAA	TTTGAAAAGCCTACACGACGGCGAA
18	TGTTCCCAGTGAAGCTGCGATCTGG	TCCAGATCGCAGCTTCACTGGGAAC
19	TTACTTGGCATGGAATCCCTTACGC	TGCGTAAGGGATTCCATGCCAAGTA
20	TACTAGCATATTTCAGGGCACCGGC	TGCCGGTGCCCTGAAATATGCTAGT
301	TCCCGATATTCGCCCGGCCTATTCG	TCGAATAGGCCGGGCGAATATCGGG
302	TCGAGAAGATGCCTCACGCAACCAA	TTTGGTTGCGTGAGGCATCTTCTCG
303	TAACCTTGACCCGTGGATGACGCTA	TTAGCGTCATCCACGGGTCAAGGTT
6	TTTGCAACGGGCTGGTCAACGTCAA	TTTGACGTTGACCAGCCCGTTGCAA
7	TCGCATAGGTTGCCGATTTCGTCAA	TTTGACGAAATCGGCAACCTATGCG
306	TGCTTCCGGATGAACGGGATGGTTG	TCAACCATCCCGTTCATCCGGAAGC
307	TCCCTCCATGTTCTTCGAACGGTTT	TAAACCGTTCGAAGAACATGGAGGG
308	TTTGATGGGCGGCAATGCTCTTGCT	TAGCAAGAGCATTGCCGCCCATCAA

Illumina attempt to re-patent Zirvi-Barany's *exact* zip code sequences; accidentally leaves one with wrong ID in Table 1, includes all in Table 2, and has them in a bizarre order in tables 3 & 4.

Illumina submits provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000:

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number: EK916735211US Date of Deposit: August 25, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box PROVISIONAL APPLICATION, Assistant Commissioner for Patents, Washington, DC 20231. on August 25, 2000

Typed or Printed Name: Vince Diaz

Signed:

Docket Number:	P-69605/DJB/RMS/DCF	Type a plus sign (+) inside this box →

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
CHEE	MARK	S.	Del Mar, California
GUNDERSON	KEVIN		Encinitas, California

TITLE OF THE INVENTION (280 characters max)

PROBES AND DECODER OLIGONUCLEOTIDES

TABLE 2

IllumaCode ID	Decoder Sequence (5'-3')	Probe Sequence (5'-3')
1	TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA
2	TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA
3	AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT
4	CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG
5	ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT
6	TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA
7	CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG
8	CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG
9	TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA
10	GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC
11	TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA
12	CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG
13	GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC
14	AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT
15	CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG
16	CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG
17	GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC

Full Appl., (K. Gunderson) on August 27, 2001

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2002 (28.02.2002)

PCT

(10) International Publication Number
WO 02/16649 A2

(51) International Patent Classification[7]: C12Q 1/68

(21) International Application Number: PCT/US01/26519

(22) International Filing Date: 27 August 2001 (27.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/227,948 25 August 2000 (25.08.2000) US
60/228,854 29 August 2000 (29.08.2000) US

(71) Applicant: ILLUMINA, INC. [US/US]; Suite 200, 9390 Towne Centre Drive, San Diego, CA 92121 (US).

(72) Inventor: GUNDERSON, Kevin; 1543 Juniper Hill Drive, Encinitas, CA 92024 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— without international search report and to be republished upon receipt of that report

TABLE 2

Seq. ID No.	Decoder Sequence (5'-3')	Probe Sequence (5'-3')
1	TTCGCCGTCGTGTAGGCTTTTCAA	TTGAAAAGCCTACACGACGGCGAA
2	TTCGAAGCGCACGTCCCTTTTCAA	TTGAAAAGGGACGTGCGCTTCGAA
3	AACGCGTGGGGAATGGGACATCAA	TTGATGTCCCATTCCCCACGCGTT
4	CCGTCGCATACCGGCTACGATCAA	TTGATCGTAGCCGGTATGCGACGG
5	ATGGCCGTGCTGGGGACAAGTCAA	TTGACTTGTCCCCAGCACGGCCAT
6	TTGCAACGGGCTGGTCAACGTCAA	TTGACGTTGACCAGCCCGTTGCAA
7	CGCATAGGTTGCCGATTTCGTCAA	TTGACGAAATCGGCAACCTATGCG
8	CCGTTTGCGGTCGTCCTTGCTCAA	TTGAGCAAGGACGACCGCAAACGG
9	TTCGCTTTCGTGGCTGCACTTCAA	TTGAAGTGCAGCCACGAAAGCGAA
10	GTCCAACGCGCAACTCCGATTCAA	TTGAATCGGAGTTGCGCGTTGGAC
11	TTGCCGCACCGTCCGTCATCTCAA	TTGAGATGACGGACGGTGCGGCAA
12	CATCGTCCCTTTCGATGGGATCAA	TTGATCCCATCGAAAGGGACGATG
13	GCACGGGAGCTGACGACGTGTCAA	TTGACACGTCGTCAGCTCCCGTGC
14	AGACGCACCGCAACAGGCTGTCAA	TTGACAGCCTGTTGCGGTGCGTCT
15	CGTGTAGGGGTCCCGTGCTGTCAA	TTGACAGCACGGGACCCCTACACG
16	CATCGCTGCAAGTACCGCACTCAA	TTGAGTGCGGTACTTGCAGCGATG
17	GGCTGGTTCGGCCCGAAAGCTTAG	CTAAGCTTTCGGGCCGAACCAGCC

Illumina attempt to re-patent Zirvi-Barany's *exact* zip code sequences; changes "IllumaCode ID" to "Seq. ID No.", and drops Mark Chee as inventor when moving from provisional to full application. What are they trying to hide?

Illumina submits full application 09/940,185 = WO 2002016649 on August 27, 2001.

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2002 (28.02.2002)

PCT

(10) International Publication Number
WO 02/16649 A2

(51) International Patent Classification[7]: C12Q 1/68

(21) International Application Number: PCT/US01/26519

(22) International Filing Date: 27 August 2001 (27.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/227,948 25 August 2000 (25.08.2000) US
60/228,854 29 August 2000 (29.08.2000) US

(71) Applicant: ILLUMINA, INC. [US/US]; Suite 200, 9390 Towne Centre Drive, San Diego, CA 92121 (US).

(72) Inventor: GUNDERSON, Kevin; 1543 Juniper Hill Drive, Encinitas, CA 92024 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— without international search report and to be republished upon receipt of that report

WO 02/16649 A2

(54) Title: PROBES AND DECODER OLIGONUCLEOTIDES

(57) Abstract: The present invention is directed to improved methods and compositions for the use of adapter sequences on arrays in a variety of multiplexed nucleic acid reactions, including synthesis reactions, amplification reactions, and genotyping reactions.

Illumina submits full application of "Probes and Decoder Oligonucleotides" on August 27, 2001, which deletes the words "**universal arrays**" in the abstract to the patent office.

1. **Adapter molecules and universal arrays and their use in detection of targets**
Quick View
By Gunderson, Kevin
From PCT Int. Appl. (2002), WO 2002016649 A2 20020228. | Language: English, Database: CAPLUS

Adapter molecules and universal arrays and their use in detection of targets

By: Gunderson, Kevin
Assignee: Illumina, Inc., USA

The present invention is directed to improved methods and compns. for the use of adapter sequences on arrays in a variety of multiplexed nucleic acid reactions, including synthesis reactions, amplification reactions, and genotyping reactions. Thus, a method for immobilizing target nucleic acids comprises attaching an adapter nucleic acid to a target nucleic acid to form a modified target nucleic acid, then contacting this modified nucleic acid with an array of at least 25 different addresses, each address contg. a different adapter probe. Further, a method for detecting target nucleic acids makes use of these immobilized target nucleic acids by providing a means of detecting the immobilized target mols. The use of adapter nucleic acids allows one to prep. "universal arrays", the capture probes of which can be modified by different adapter nucleic acids depending upon the use to which it is to be applied.

Illumina attempt to re-patent Zirvi-Barany's *exact* zip code sequences; deletes the words "**universal arrays**" in the abstract to the USPTO, in an effort to hide that Illumina's application is really the intellectual property of WO97/31256, i.e. the "Zip Code Chemistry" invented by the Barany lab.

Illumina own provisional patent application shows that Universal Bead Arrays are Zip Code Arrays.

Illumina 60/180810 Provisional, Filed Feb. 7, 2000

02/07/00 jc688 U.S. PTO

02-09-00 A/PRov

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number EL406567991US, Date of Deposit February 7, 1999

I hereby certify that this paper or fee and listed enclosures is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231, on February 7, 1999

Typed or Printed Name: HAMMID SANCHEZ

Signed:

Docket Number: P-68929/DJB/RMS/DCF | Type a plus sign (+) inside this box →

JC533 U.S. PTO 60/180810 02/07/00

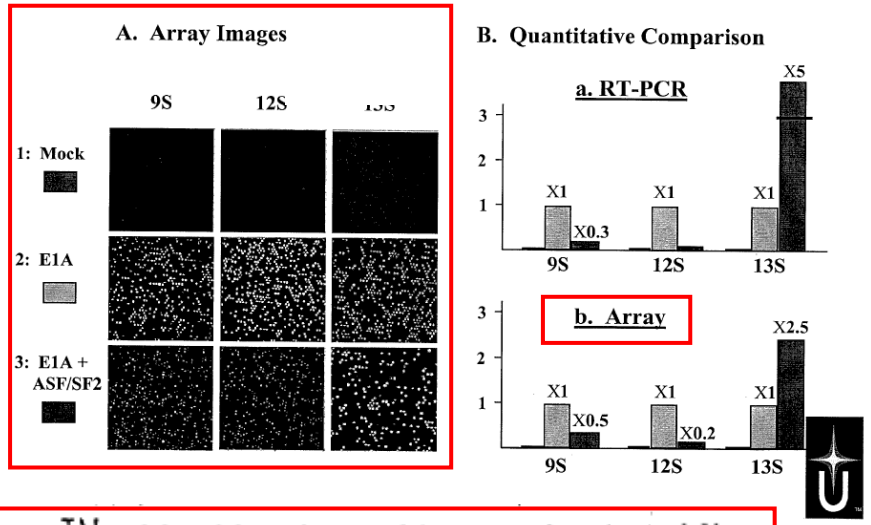
INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
FAN	Jian-Bing		San Diego, California

TITLE OF THE INVENTION (280 characters max)

GENE EXPRESSION PROFILING

Detection of Alternative Splicing on Zip-Code Arrays and Comparison with RT-PCR

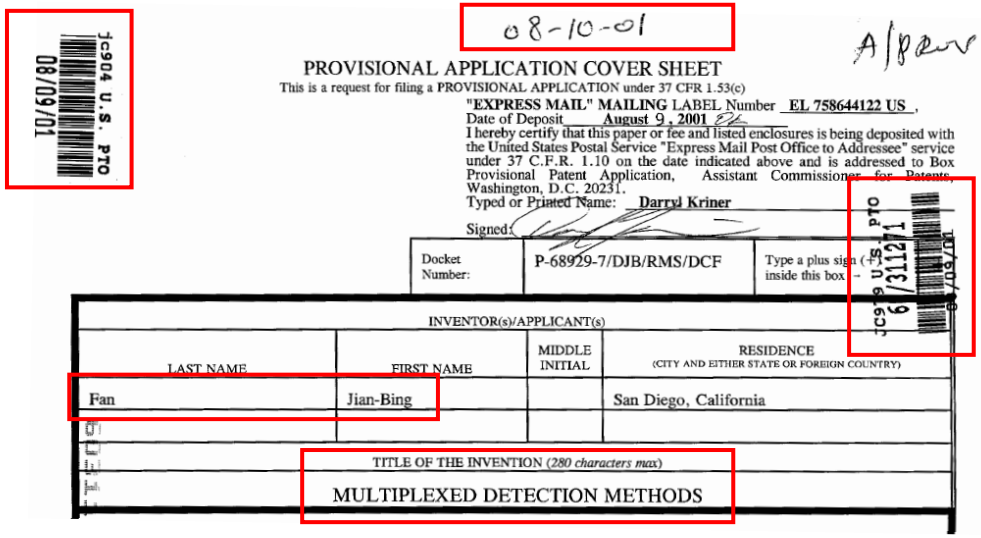


Currently, Illumina has developed universal BeadArrays™ with 128 unique addresses that hybridize efficiently and with high specificity. Development of arrays with up to 2,000 addresses is in progress. In

Illumina admits – 4 years after Barany Lab's zip code patent was filed – that "Illumina has developed **Universal** BeadArrays with 128 unique addresses that hybridize efficiently and with high specificity". Such "**Universal** BeadArrays" are called Zip-Code Arrays and shown to work in their last figure, which tellingly is deleted from all subsequent patent applications from this patent family.

Illumina attempts to hastily rename probes containing zip codes as "adapters".

Illumina Provisional 60/311,194, Filed Aug. 9, 2001



08-10-01

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number EL 758644122 US

Date of Deposit August 9, 2001

I hereby certify that this paper or fee and listed enclosures is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Typed or Printed Name: Darryl Kriner

Signed:

Docket Number:	P-68929-7/DJB/RMS/DCF	Type a plus sign (+) inside this box →

INVENTOR(s)/APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Fan	Jian-Bing		San Diego, California

TITLE OF THE INVENTION (280 characters max)

MULTIPLEXED DETECTION METHODS

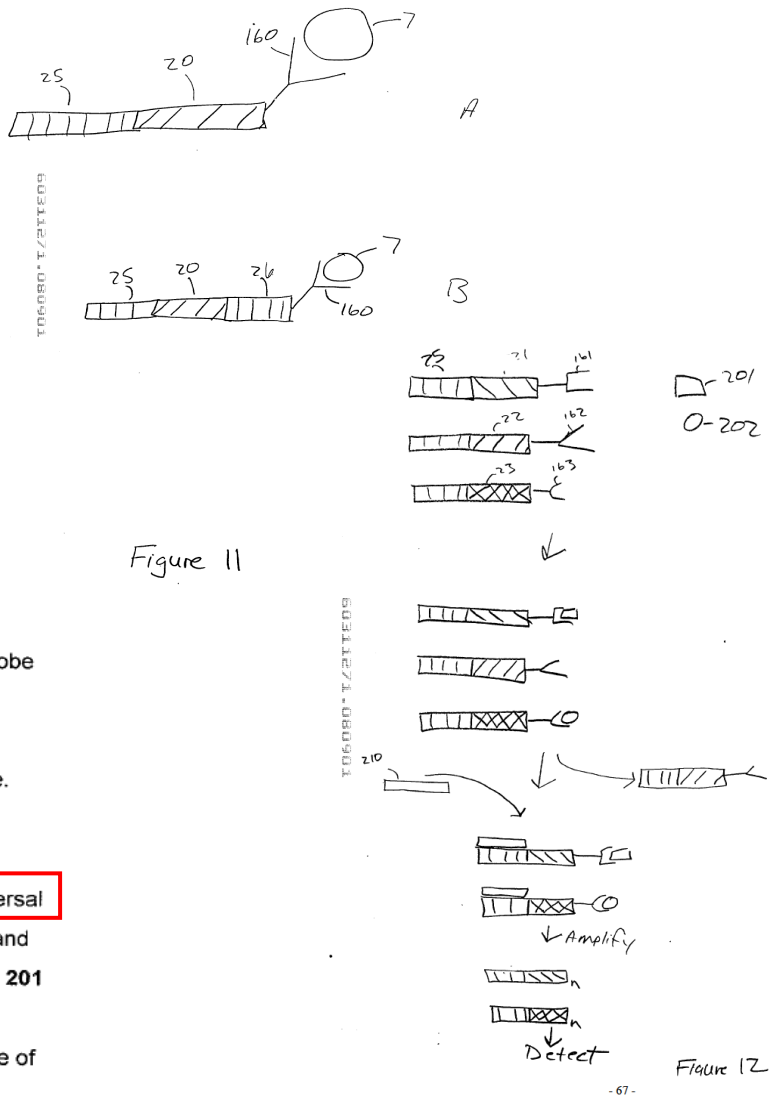


Figure 11 depicts two configurations of probes for multiplex detection of analytes. A depicts a probe containing an adapter **20**, an upstream priming site **25** and a target-specific portion, i.e. bioactive agent **160** bound to a target analyte **7**. B depicts a probe containing an adapter **20**, an upstream universal priming site **25**, a downstream universal priming site **26** and a target-specific portion, i.e. bioactive agent **160** bound to a target analyte **7.**

Figure 12 depicts a preferred method for multiplex detection of analytes. Probes containing universal priming sequence **25** and adapters that identify the target analyte to be detected **21, 22 and 23**, and target specific portions, i.e. bioactive agents **161, 162 and 163** are contacted with target analytes **201 and 202**. Probes to which target analytes bind are contacted with universal primers **210** and amplification reaction mixture. Amplicons are detected and serve as an indication of the presence of the target analyte.

- 67 -

Illumina hastily submits provisional 60/311,194 on Aug. 9, 2001, tries to rename probes containing zip codes, universal priming sequences, and target sequences as "adapters"

Illumina Makes Further Use of Barany Lab's Intellectual Property and Exact Zip Codes, and Uses Seventeen Different Alternative Names, to Obfuscate the Origin of Zip Codes to the USPTO and the Court

The term "zip code" enters Illumina patent applications only after JDA signed with PEB on November 9th, 1999

60090473 as originally filed on June 24, 1998
- All figures relate to using enzymes or antibodies on the surface of beads, none were retained in final application.

09189543 as originally filed on Nov. 10, 1998
- This version has no examples and no figures, and no explanation of decoding. No mention or thought of zip codes.

09344526 as originally filed on June 24, 1999 = US7060431
- This version has no examples and no figures, and no explanation of decoding. No mention or thought of zip codes.

60172106 as originally filed on Dec. 23, 1999
- Illumina officially begins collaboration with PE-Biosystems on 11-9-1999 – which had access to confidential Zirvi-Barany 465 set Zip codes and Zirvi-Barany Intellectual Property including trade secrets
- Example 1 and Figure 1 now show for the first time; decoding arrays, clearly using zip code idea, but deliberately concealed the sequence of oligonucleotides used and the actual hybridization and wash conditions they used.

60235531 as originally filed on Sept. 26, 2000
- Similar to above, highlight success of error correction, which is solely dependent on using zip code sequences.

09748706 as originally filed on Dec. 22, 2000 = US7033754
- Propose primer-extension approach to decode arrays, no evidence this ever worked. They accidentally use the words "zip code loci" in example 6. Imagine if Samsung had used the word "iPhone" in their patents with no explanation.

60302213 as originally filed on June 28, 2001
- No new examples provided, but some hastily thrown together figures speculating use of reversible terminators for decoding, in combination with zip codes. An exonuclease approach for decoding is described, but it will not work. Illumina plagiarizes the word "zipcode" zip code" or "cZip" 16 times, without ever defining the words.

10187321 as originally filed on June 28, 2002 = US7226734
- No new examples, but one new figure is provided with no data. The figure reveals that approximately 1520 beads were correctly decoded – this matches the 1536 – 16 = 1520 functional bead types in the Gunderson et. al 2004 paper wherein the same data was derived by serial hybridization of pools to zip code oligonucleotides onto the addressable arrays.

The term "zip code" enters Illumina patent applications only after IDA signed with PEB on November 9th, 1999

terminator colors. After the reaction is over the array tip is imaged to capture the color of the beads at this stage. Beads are then immediately stripped of color or label by denaturing and washing off the first extended primer at each zip code loci. This process can be repeated through multiple stages. In subsequent stages, the primer extension reactions contain the same reagents as the previous extension reaction except

09748706 as originally filed on Dec. 22, 2000: Illumina lawyers probably instructed inventors to remove the word "**zipcode**" from the patent application, but in their rush, they missed "**zip code loci**" in example 6, because it has a space between "**zip**" and "**code**". No explanation given for the term.

60302213 as originally filed on June 28, 2001: Illumina lawyers probably figured the collaboration with PE-Biosystems is going well, so left in "zipcode", "zipcodes", "zip code loci" "zip codes" and "cZip".

Figure 13 Depicts construction of probes on bead containing encoding sequences, zipcodes, and a gene-specific sequence. Two different encoding cassettes are employed to facilitate the primer extension reaction using primers with universal or degenerate bases. Using four color sequencing and a single base code, 6 bases generates 4^6 = 4096 codes, likewise four color hybridization using single hybridization colors also generates 4096 codes. The grand total number of codes is 4096*4096 = >16 million. If only a single color/two state scheme is employed for hybridization, than 2^6 = 64 codes are generated. The grand total is 4096*64 = 262,144 codes. The zipcode sequences can also be constructed so as to be overlapping to reduce the length of the overall sequence (i.e. cZip#1 vs. cZip#2).

09748706 as originally filed on Dec. 22, 2000 = US7033754

- Propose primer-extension approach to decode arrays, no evidence this ever worked. They accidentally use the words "zip code loci" in example 6. Imagine if **Samsung** had used the word "**iPhone**" in their **patents with no explanation**.

60302213 as originally filed on June 28, 2001

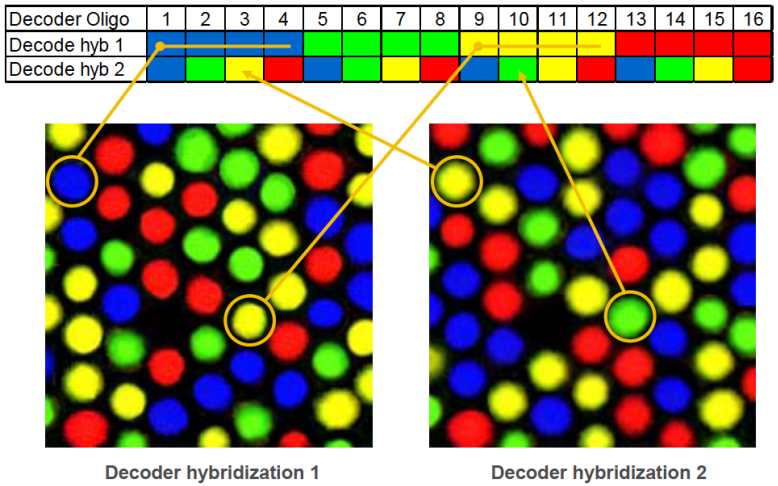
- No new examples provided, but some hastily thrown together figures speculating use of reversible terminators for decoding, in combination with zip codes. An exonuclease approach for decoding is described, but it will not work. Illumina plagiarizes the word "zipcode" zip code" or "cZip" 16 times, without ever defining the words.

Illumina's Proprietary Software Retains Fingerprints of Zip Code Inventors Intellectual Property

DMAP files are collections of Zip codes/Capture Oligonucleotides 1

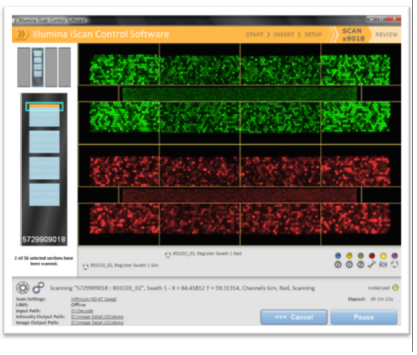
Bead Decoding

Example: 16 Bead Types

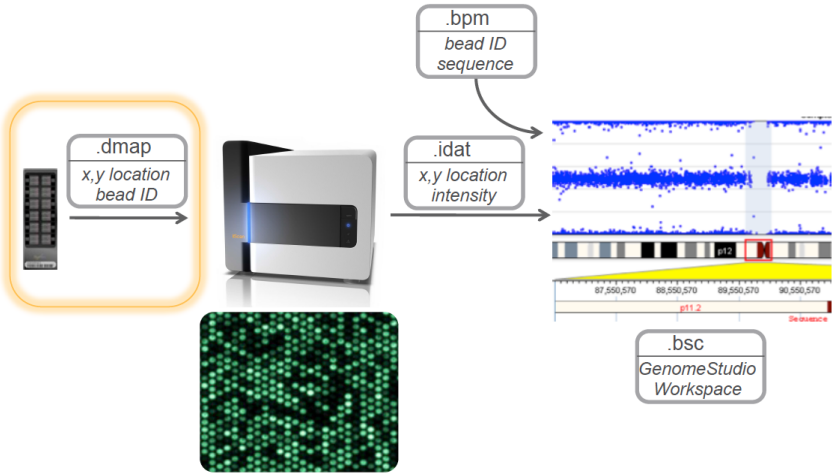


iScan Control Software

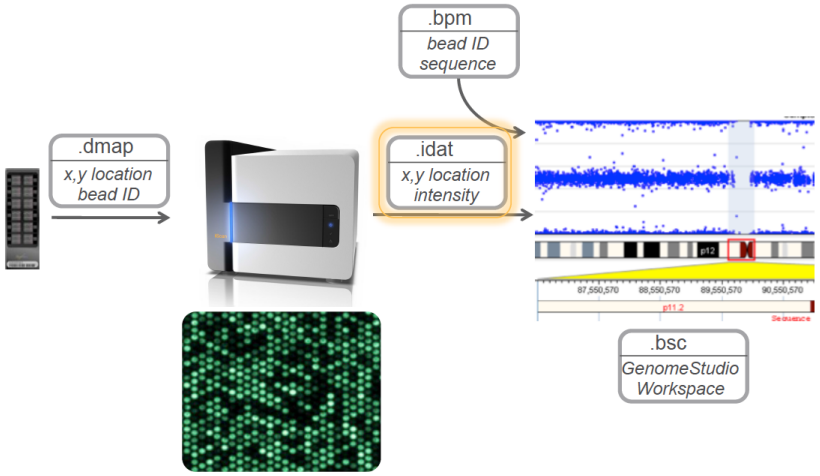
Applications flexibility	• Infinium • GoldenGate • Gene Expression • Methylation
Simple Operation	• Intuitive iScan control software for BeadChips
Automated	• Auto scan • Auto error checking



Collecting Data from a BeadChip: DMAPs



Collecting Data from a BeadChip: .idat



David Walt testimony on March 6, 2013 at Syntrix trial:

A. It's two-dimensional, because you can specify the location of any bead just by defining two dimensions: an X-dimension and a Y-dimension. So that will tell you exactly where each bead is. And the only way that one can do that is with something that is planar.

Q. It may have been clear to some, but not all. You describe here the arrangement of the beads on the top of a fiberoptic bundle as two-dimensional. If those beads were laid out on a silicon or a glass or a plastic slide, one of those substrates as described in your patent, would that be two-dimensional or a three-dimensional configuration?

A. That would be two-dimensional.

MR. ROSENBAUM: No further questions.

David Walt admits that one needs to specify the location of each bead just by defining two dimensions: an X-dimension and a Y-dimension. In other words the location of each bead is defined before use.

Why is the term "ZipCode" in Illumina's software? Part 2

The term "ZipCode" is used as a variable in multiple areas for software to identify/decode beads with XY addresses, just as in Universal Zip Code arrays as described by Barany Lab IP. It means that Illumina programmers thought of the sequences as "ZipCode" sequences in DMAP files used by Illumina.

There is no "area code" or "phone number" in any of the .dll files. There is also a parameter in the ZipCode data structure titled "ExcludeFromObfuscationAttribute" indicating they were trying to keep this data secret.

In File IlmnDataFiles.dll:

Int16 DESCryptoServiceProvider SymmetricAlgorithm set_Mode PaddingMode set_Padding set_IV set_Key ICryptoTransform CreateEncryptor CryptoStream CryptoStreamMode FlushFinalBlock WriteByte FileNotFoundException ReadByte CreateDecryptor get_Position FileLoadException NotSupportedException SetLength **ExcludeFromObfuscationAttribute** RuntimeTypeHandle GetTypeFromHandle System.Xml.Serialization XmlSerializer Serialize get_BaseStream IsNaN Deserialize ReadChars GetFileName ReadInt16 Read

Int64 BackgroundMean BackgroundStdDev **ZipCode** StdDev Mean Median NumNonOutlierBeads TrimmedMean Read

In File CommonVeraScan.dll:

LARGE_INTEGER **ZipCode** CoreData CoreDataArray CoreStatus Sorting EventRecursionBlocker EventBarrier RegistrationFormat RegistrationModeEnum RegistrationScoreStruct RegistrationParameters Polynomial Illumina.Common.LinearAlgebra IMatrix ICholeskyDecomposition ILuDecomposition IQrDecomposition ISingularValueDecomposition IEigenvalueDecomposition Matrix CholeskyDecomposition LuDecomposition QrDecomposition SingularValueDecomposition EigenvalueDecomposition MathHelper ILog Illumina DriveType DiskSpaceInfo VolumeInfo SystemUtils MathSupportFunctions ImageChangedEventArgs ImageSizeChangedEventArgs ImageSizeChangedEventHandler VisibilityChangedEventHandler IImageBase XYZIntPoint ProfileEventHandler Profiler ClonedProfilerData ProfileContextValue ProfileContextData ProfileContext Filename AdditionalContextException MultiException TransformationType Transformation TransformAttributes ProfileEvent EventType ProfileEventArgs EventsHelper AsyncFire mscorlib System ValueType Object Enum ICloneable EventArgs TEventArgs MulticastDelegate IDisposable Attribute ApplicationException X Y .ctor LoadLocations SaveLocations Z System.Drawing PointF GetHashCode Equals op_Equality op_Inequality String IsActualVersionA_AtLeast_TargetVersionB _Value value__ Synchronous Asynchronous GreenCY3 RedCY5 BeadEnd DistalEnd ArrayMatrix

Drawing2D ToAltString CalculateOrthogonality Invert TransformPoints TransformPoint TransformVectors TransformVector Transform InverseTransform Invert3x3 ConvertArray invert3x3 mult3x3WithVec mult3x3 Multiply3x3Precise CreateMatrix CreateTransformation CreateTransformationRobust Elements XOffset YOffset Rotation XScaling YScaling Shear Timestamp Type Context ActivityName ActivityFullName get_Event _event AsyncFireCleanUp Delegate InvokeDelegateBlocking InvokeDelegateHybrid FireEventBlocking FireEventAsync x y FilePath Locs OutputPath z orig obj left right actualVersionA featureVersionB numberOfSignificantSegments okIfUndefinedVersionA

resultIfUndefinedVersionA **zipcode** Xvalues Yvalues slope intercept System.Runtime.InteropServices OutAttribute list mad sortedList stddev sortedValues p lowerBound upperBound xyCoords zCoords.

Why is the term "ZipCode" in Illumina's software? Part 1A

"DMAP files identify bead locations on your BeadChip and quantify the signal associated with each bead."

DMAP Files

Identify bead locations on your BeadChip and quantify the signal associated with each bead.

Effective date: October 2012*

Concurrent with the upgrade of the Decode File Client to version 3.0, the retention policy for the DMAP files has been expanded to incorporate Illumina's continuing goal of world-class support and responsiveness to customer feedback.

DMAPs will be available a minimum of 12 months from the manufacturing date**, which corresponds to the maximum time from manufacturing to expiration for our current BeadChips. During this time, customers can download the DMAPs as many times as they wish and the files will not be deleted.

We are aware that some customers may wish to have the DMAPs available even after the arrays have expired. Although it is not advisable to run Illumina BeadChips after their expiration, the DMAPs that were not downloaded during the initial 12-month period will remain available for up to an additional 12-months (2-years from manufacturing). The only exception will be if the DMAPs are successfully dow time frame. In this case, the DMAPs will be removed and unavailable for dow successful download.

*Files created before this date are only available for 13 months from the date
**Manufacturing dates can be found on BeadChip packages

DMAP Decode File Download Utility v3.0.2

Instructions for installing and using the DMAP Download Client Utility to download DMAP files.

- Decode File Client Setup 64 3.0.2 - Unzip and launch to install. Do not uninstall any previous versions of the client.
- DMAP DLL Files - For the error "Error validating \xxx .dmap gz," refer to the installation instructions.

Files

FILE NAME
Decode File Client Setup 64 v3.0.2
DMAP DLL Files
Decode File Client v3.02 Software Release Notes
DMAP Decode File Client User Guide (11337856 C)
System Requirements for DMAP Decode File Download Utility v3.0.2

Why is the term "ZipCode" in Illumina's software? Part 1B

Each BeadChip requires the user to download a DMAP file for that array.

Finding BeadChip DMAP Files in Access by Account Mode

Access by Account mode enables you to download any DMAP files that you have purchased within the last 12 months through your MyIllumina account.

Access by Account Mode Tabs

In Access by Account mode, you will be able to see and use the Main, Download Status and Log, Alerts, SMTP Test, and Help tabs:

- **Main tab:** Enables you to find and download BeadChip DMAP files.
- **Download Status and Logs tab:** Enables you to view download progress and status, abort the download, and save a download log to a file.
- **Alerts:** When AutoPilot is selected on the Main tab, enables you to enter contact names and email addresses to which messages will be sent based on the parameters you select. You can have Decode File Client send you email notifications for the following conditions: job start, job finish, and errors. Each line in the table enables you to send out a message to one email for one type of condition. If you want to send emails to multiple email addresses, you can add multiple email addresses. If you want to send emails for different conditions to the same email address, you can enter the email address several times and select one condition for each instance.
- **SMTP Test:** Enables you to set SMTP parameters for alerts messaging.
- **Help tab:** Enables you to read the user help for the Decode File Client.

Selecting and Downloading BeadChip DMAP Files

Before downloading BeadChip DMAP files, ensure that you have enough free space on your computer's download destination.

To download the DMAP files from the list of found BeadChips, do the following:

View Available DMAP Files

1 On the **Main** tab, select one of the following options:

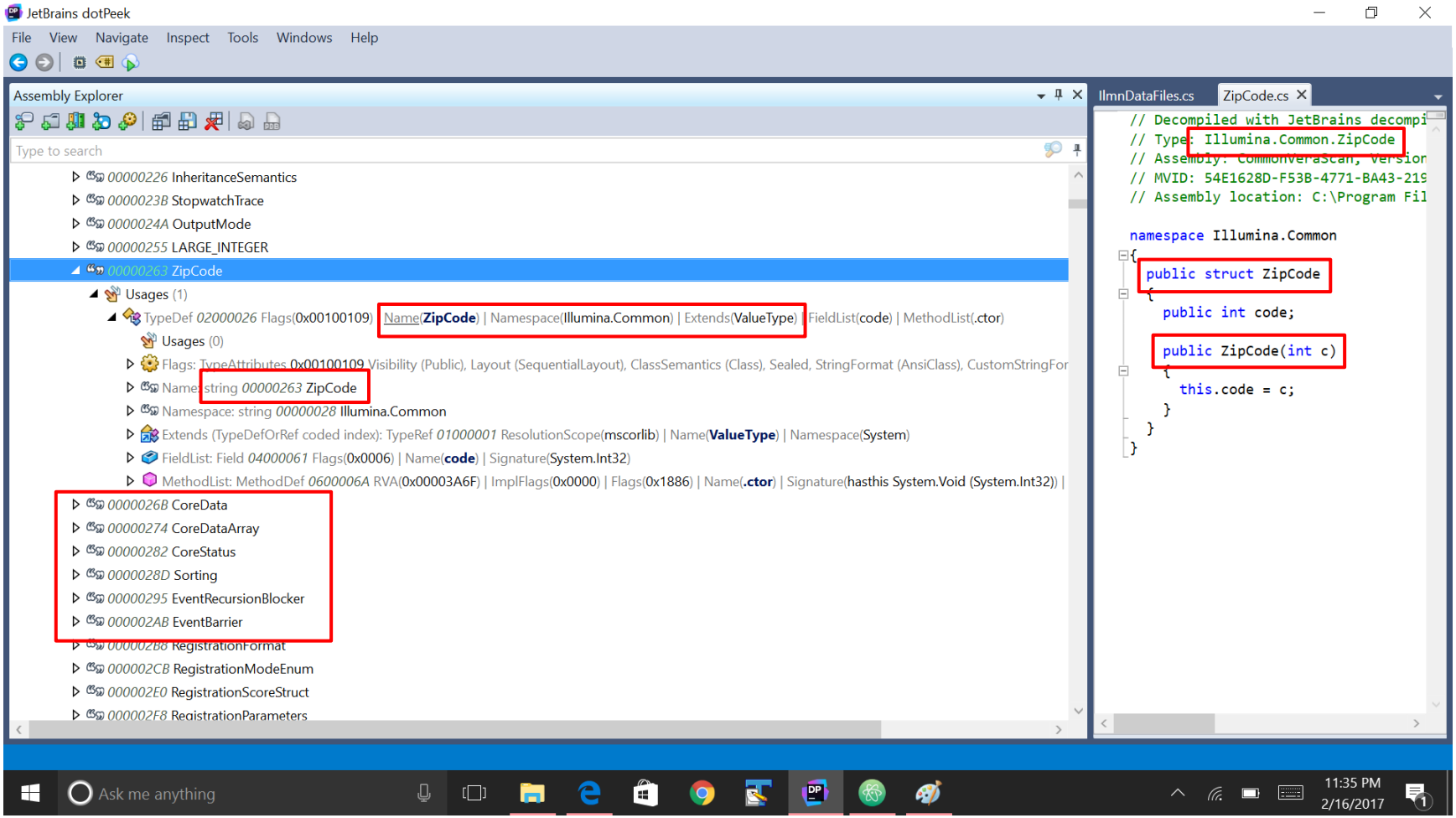
Option	Use
AutoPilot	Automatically checks for new DMAP files and downloads them as they become available. AutoPilot is set to check for new BeadChip decode files every 24 hours. To use AutoPilot, you will need to specify your SMTP server (using the SMTP Test tab) and set up an alert (using the Alerts tab).
All my BeadChips that have NOT been downloaded	Displays all serial numbers that have not yet been downloaded
All my BeadChips	Displays a list of all BeadChip serial numbers that you have ordered and that are available for download
BeadChips by Purchase Order	Displays all of the serial numbers that are associated with a specific PO# and are available for download
BeadChips by barcodes	Displays only the serial numbers for barcodes entered in the dialog. You may copy and paste or scan barcodes directly into the dialog box.

2 If you have selected BeadChips by Purchase Order or BeadChips by barcode, enter one or more purchase order numbers or barcodes respectively. If you have multiple purchase order numbers, enter them in the text box, separated by commas. If you have multiple barcodes, enter one per line.

3 Click **Find**. The Decode File Client displays a list of available BeadChip barcodes.

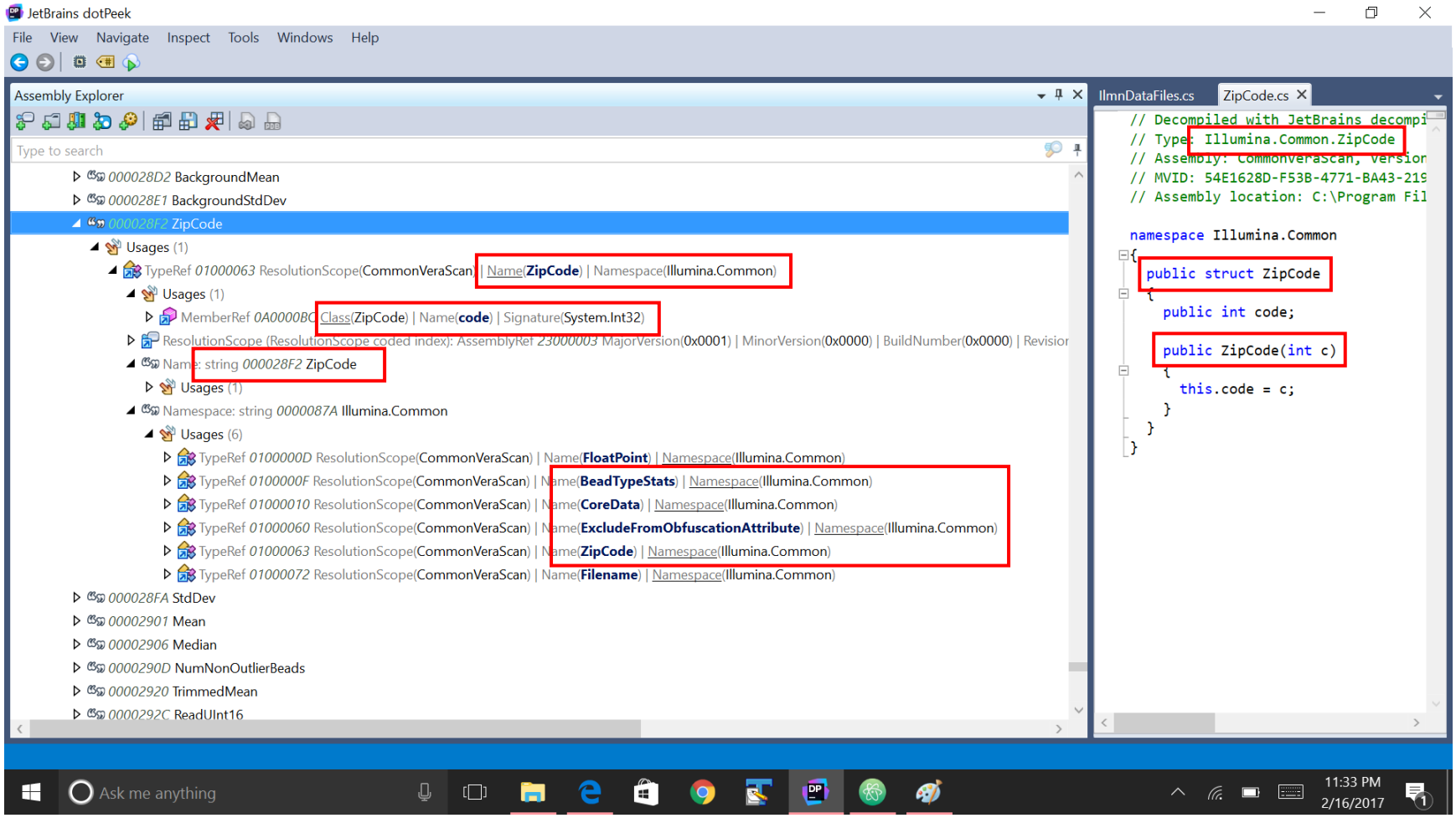
Why is the term "ZipCode" in Illumina's software? Part 4

Screenshot showing data structures labeled ZipCode in multiple places in these two important Dynamically Linked Libraries (.dll files) used by the DMAP software critical for determining the location of beads on a BeadChip and other Illumina arrays.



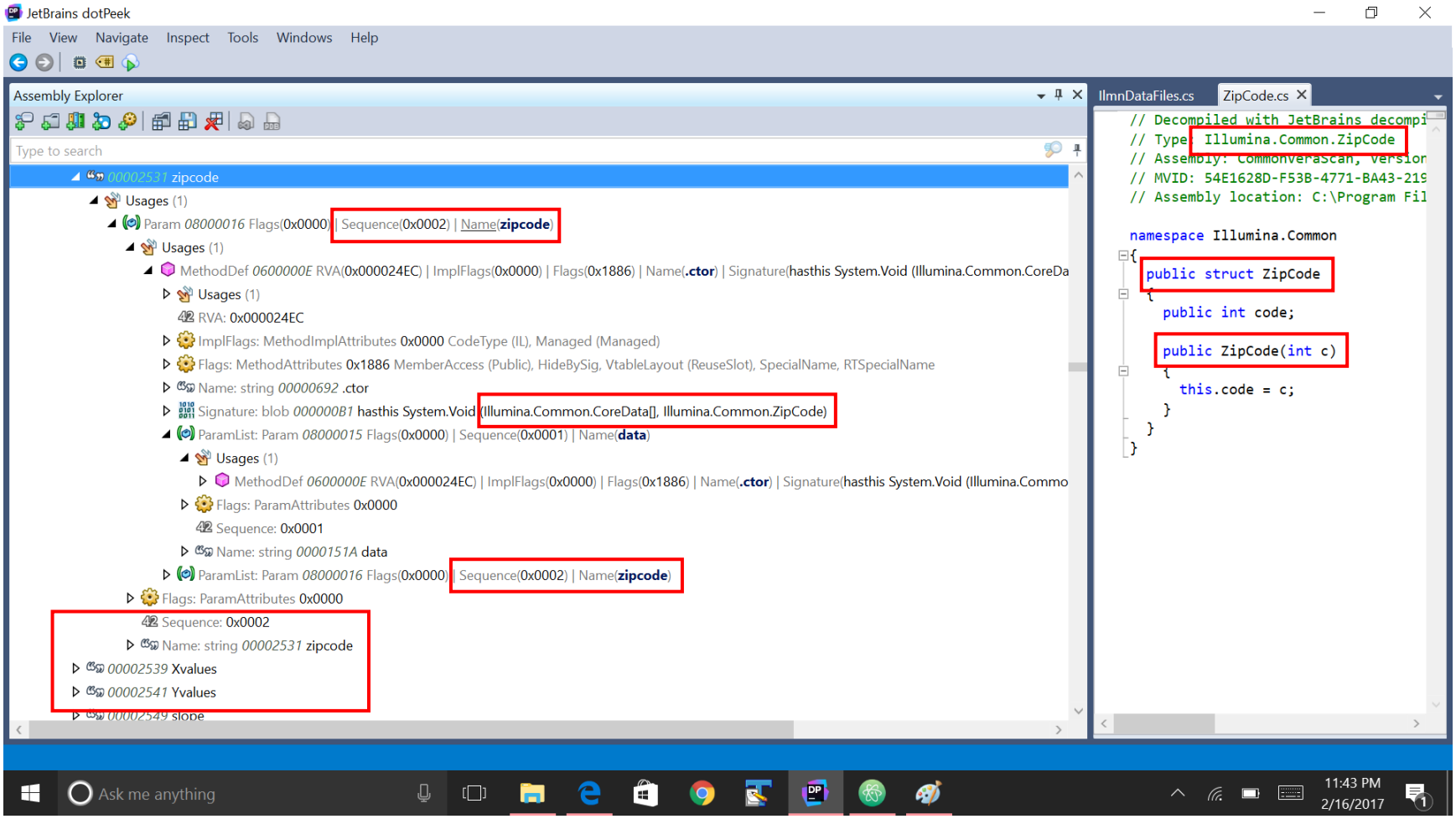
Why is the term "ZipCode" in Illumina's software? Part 3

Screenshot showing data structures labeled ZipCode in multiple places in these two important Dynamically Linked Libraries (.dll files) used by the DMAP software critical for determining the location of beads on a BeadChip and other Illumina arrays.



Why is the term "zipcode" in Illumina's software? Part 5

Screenshot showing data structures labeled "ZipCode" and "zipcode" in multiple places in these two important Dynamically Linked Libraries (.dll files) used by the DMAP software critical for determining the location of beads on a BeadChip and other Illumina arrays. This even lists "X values" and "Y values" right after the word "zipcode".



Illumina's Own FOIA Request to the NIH on Illumina's Grant Applications Triggers the True Inventors to Follow Illumina's Trail

Illumina unusual January 05, 2015 FOIA request for copies of its own grants:

Bartok, Lauren (NIH/OD) [C]

From: Noon, Will <wnoon@illumina.com>
Sent: Monday, January 05, 2015 7:16 PM
To: NIH FOIA
Subject: Freedom of Information Act Request

Hello,

I would like to request a copies of some funded grant applications under the Freedom of Information Act (FOIA). The grant information is below:

Project Number: 1R21HG001911-01 (Former Number 1R01HG001911-01)
Title: RANDOMLY ORDERED DNA ARRAYS FOR SNP DISCOVERY AND TYPING
Project Leader: Chee, Mark S.
Awardee Organization: Illumina, Inc.

Project Number: 1R44HG002003-01
Title: RANDOMLY ORDERED DNA ARRAYS FOR SNP GENOTYPING
Project Leader: Chee, Mark S.
Awardee Organization: Illumina, Inc.

Project Number: 1R43CA081952-01
Title: GENE EXPRESSION ANALYSIS ON RANDOMLY ORDERED DNA ARRAYS
Project Leader: Chee, Mark S.
Awardee Organization: Illumina, Inc.

Project Number: 1R43CA083398-01
Title: PARALLEL ARRAY PROCESSOR
Project Leader: Chee, Mark S.
Awardee Organization: Illumina, Inc.

I am an in-house attorney at Illumina, Inc., the awardee organization for all of these grants, and therefore am requesting this document on behalf of the awardee. Illumina, Inc. approves of the release of the grant application, solely to *Illumina, Inc., without any redactions.* **If a FOIA request is not the correct procedure for an awardee to request a copy of their own grant application, please let me know what the appropriate procedure would be.**

My contact information is:

William Noon
Illumina, Inc.
5200 Illumina Way
San Diego, CA 92122
Phone: 858-202-4780
Email: wnoon@illumina.com

I am willing to accept electronic copies of the documents via email.

If you have any questions or require further information, please let me know. Thank you in advance for your assistance.

Illumina: Fan SBIR 1R43CA097851-01 Grant, submitted November 30, 2001

C.4 High Throughput SNP Genotyping on Fiber Optic Arrays

We have developed a highly multiplexed method for SNP genotyping by combining an oligonucleotide ligation-based assay (OLA) with read-out on random arrays of universal capture probes (Gerry et al., 1999) (Fig. 6). There are a number of advantages of this assay system, outlined below.

Universal Array. By designing the assay system to use arrays of universal capture probes, many different sets of SNPs or methylation target sequences can be analyzed using a standard array. This provides a great deal of flexibility, and also reduces costs. The universal array contains probes that are sufficiently long to hybridize with high specificity. Similar approaches have been used in parallel analyses of yeast deletion strains (Shoemaker et al., 1996; Winzeler et al., 1999) and SNP genotyping (Fan et al., 2000; Gerry et al., 1999).

Sequence Specificity. The oligo ligation assay requires two different oligonucleotides to hybridize contiguously before ligation can occur. In addition, the ligase enzyme discriminates against even a single base mismatch in the vicinity of the ligation site. This built-in specificity improves the ability to analyze complex genomic samples accurately. Complex samples, such as human genomic DNA, contain many similar sequences and hence provide more opportunities for incorrect hybridization.

Multiplexing. The design of the assay is such that the oligo ligation step occurs first, on genomic DNA, and is then followed by PCR using universal primers incorporated in the ligation oligos (Fig. 6). This is in direct contrast to most other genotyping approaches, in which PCR amplification occurs first. Because the approach shown in Fig. 6 uses universal primers, and the PCR templates are relatively short, the robustness of multiplex PCR amplification is increased. We have been able routinely to carry out high levels of multiplexing. This is an important factor in reducing assay costs and increasing the scalability of the system.

Applicants are aware that reviewers penalize NIH grant applications that are not properly referenced. Thus, Zirvi's FOIA request reveals for the first time that Illumina's J.B. Fan admits that the highly multiplexed method for SNP genotyping is based on direct ligation of two oligonucleotides that "hybridize contiguously" with readout on "random arrays of universal capture probes", and properly cites Gerry-Barany 1999. Other than Illumina's provisional patent application 60/180810 (submitted by J.B. Fan, with an embedded grant section written by Fu, where the word "Zip code Array" was accidentally left in a Figure), Illumina consistently tried to obfuscate that their bead arrays were literally zip code arrays as described by Barany Lab in the WO97/31256 patent.

Illumina: Fan SBIR 1R43CA097851-01 Grant, submitted November 30, 2001

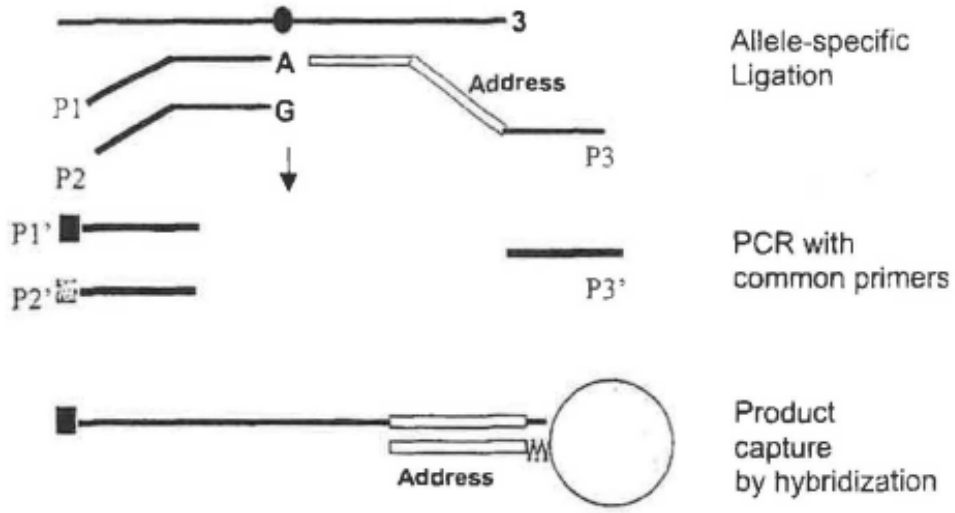


Figure 6. Schmatic of the OLA-PCR SNP genotyping assay. For each SNP, three OLA probes are designed: two allele-specific oligos, each corresponding to one allele, and one locus-specific oligo. The ASOs consist of two parts: the SNP-specific sequence and a universal PCR primer sequence (P1 or P2) at their 5'-end. The LSOs consist of three parts: the SNP-specific sequence, a unique address sequence which is complementary to a capture sequence immobilized on the array, and a universal PCR primer sequence (P3) at their 3'-end. A ligation reaction joins the ASO and LSO oligos to create a PCR template that can be amplified with universal primers (P1', P2', and P3). The ligation reaction provides allele selectivity: only if the 3' end nucleotide on the ASO matches the SNP sequence in the template is ligation carried out efficiently. The PCR products, wich are fluorescently labeled by incorporation of fluorophors at the 5' ends of P1' and P2', are hybridized to capture probes on the beads in the array. The ratio of the fluorescent signals from two allele specific ligation products indicates the genotype.

Through a FOIA request, Zirvi learns that Illumina's J.B. Fan grant application to the NIH on November 30, 2001, literally infringes on Barany Lab's LDR-PCR technology as covered in Barany Lab's '917 patent filed Feb 9, 1996, Barany Lab's '470 patent filed May 29, 1996, and Barany Lab's '293 patent filed Jan 6, 1999. It is a direct ligation (i.e. LDR) followed by PCR amplification with universal PCR primers, followed by zip-code capture on a solid support. These are outside the scope of the original Joint Development Agreement between Illumina and PE Biosystems, which only covered the IP in WO97/31256 patent ('917 series). PE Biosystems, which was responsible for overseeing the collaboration through a joint steering committee, deliberately withheld knowledge of this infringement to defraud the true inventors.

Illumina: Chee SBIR 1U54HG002753-01 Grant, submitted May 28, 2002

D.1.1 Assay Format is Designed for Multiplexing

Proprietary Info

Proprietary Info

The first step in conventional SNP genotyping is to amplify the SNP of interest from genomic DNA. In contrast, we perform an allelic discrimination step directly on genomic DNA. This is done using two allele-specific oligos, each 5' tailed with a different universal PCR priming sequence (Fig. 6). The product of this enzymatic procedure is an allele-specific PCR template. (In the case of a heterozygous DNA, both allele-specific PCR templates are produced at this step). PCR is then carried out, using only three primers (P1', P2' and P3' in Fig. 6). We have found that this procedure is amenable to high levels of multiplexing. Currently, when sufficient SNPs are available, we multiplex up to 1,152 genotyping reactions

Proprietary Info

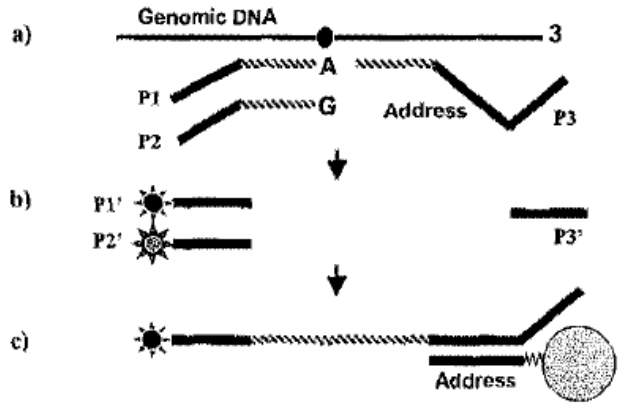


Figure 6. Assay format. a) For each SNP of interest, two allele-specific oligos and a locus-specific common oligo are annealed to genomic DNA (e.g. in a 1,152-plex reaction, a total of 3,456 oligos are annealed simultaneously, in the same reaction well in a microtiter plate). If an allele-specific oligonucleotide is complementary to the genomic DNA, a ligation product is formed. This product has universal priming sites at the 5' and 3' ends (i.e. P1 or P2, and P3). If the genomic DNA is heterozygous, then two products are formed: P1-P3 and P2-P3. **b)** Universal primers are added and PCR is carried out. The two allele-specific universal

Through a very recent FOIA request, Zirvi learns that Illumina's Mark Chee submitted a grant application to the NIH on May 28th, 2002, and Figure 6 reveals that this grant is completely based on Barany Lab's LDR-PCR technology as covered in Barany LAb's '917, '470, and '293 patent families. Illumina forgot to redact the figure legend which states "If an allele-specific oligonucleotide is complementary to the genomic DNA, a ligation product is formed" literally as described in the Barany Lab patents.

Illumina: Chee SBIR 1U54HG002753-01 Grant, submitted May 28, 2002

primers, P1' and P2' are fluorescently labeled, each with a different dye. Each amplicon contains an address that is complementary to a probe in the array, so that the genotype of each SNP can be read out on a different bead type in the array. c) The PCR amplicons are hybridized to an array of beads. The ratio of the two fluorescent signals indicates the genotype.

Another key aspect of the assay design is the incorporation of an address sequence, so that the assay products can be read out on a universal array (Chen et al. 2000; Fan et al. 2000; Gerry et al. 1999; Iannone et al. 2000). This provides flexibility. The probes on the array are random, artificial sequences that are not SNP-specific. Any set of SNPs can be analyzed simply by building the address sequences into the SNP-specific assay oligonucleotides (Section D.1.1).

Proprietary Info

Proprietary Info

genome. The use of a universal array simplifies manufacturing and reduces costs. The universal array is implemented on our BeadArray™ platform, detailed below.

D.1.2 Array Matrix Platform

The randomly ordered BeadArray technology, invented at Tufts University (Michael et al. 1998; Walt 2000), has been developed at Illumina as a platform for SNP genotyping and other high-throughput assays. Each array is assembled on an optical imaging fiber bundle consisting of about 50,000 individual fibers fused together into a hexagonally packed matrix. The ends of the bundle are polished, and one end is etched to produce a well in each fiber. This process takes advantage of the intrinsic structure of the optical fibers in the bundle (Fig. 7).

Through a very recent FOIA request, Zirvi learns that Illumina's Mark Chee submitted a grant application to the NIH on May 28th, 2002, and Figure 6 legend continued reveals that this grant is completely based on Barany Lab's LDR-PCR technology as covered in Barany Lab's '917, '470, and '293 patent families. Zirvi's FOIA request reveals for the first time that Illumina's M. Chee admits that the "assay products can be readout on a universal array" and properly cites Gerry-Barany 1999. Again, Illumina chose to redact a key sentence about the Barany Lab's Universal arrays. Since the material is over 15 years old, it is difficult to understand what would be proprietary, or suitable for a patent submission. Discovery of an un-redacted version of this application would reveal if Illumina deliberately hid information from the NIH to fraudulently obtain US government funding.

Illumina and PE Biosystems both have defrauded the True Inventors of Rightful Royalties: Appendix

Gerry-Barany JMB 1999 publication: Zip code, cZip, cZ1, Zip1, Z1.

Gerry-Barany Publication , Sept. 17, 1999

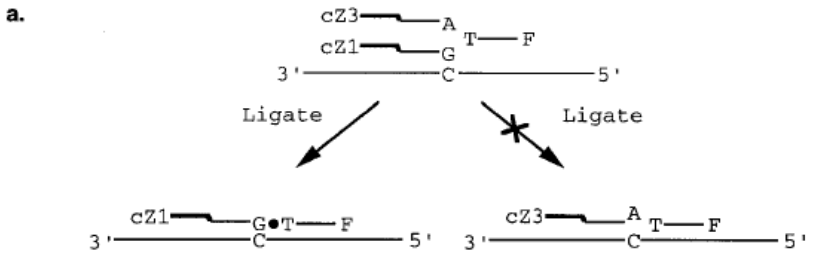
Article No. jmbi.1999.3063 available online at http://www.idealibrary.com on IDEAL® J. Mol. Biol. (1999) 292, 251–262

JMB 40

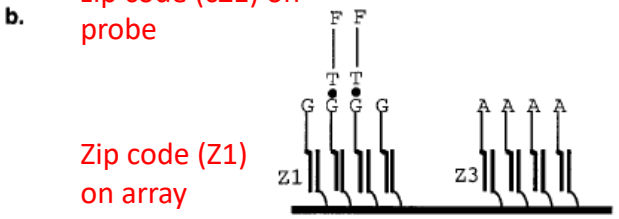
Universal DNA Microarray Method for Multiplex Detection of Low Abundance Point Mutations

Norman P. Gerry[1], Nancy E. Witowski[2], Joseph Day[1], Robert P. Hammer[3], George Barany[2] and Francis Barany[1]*

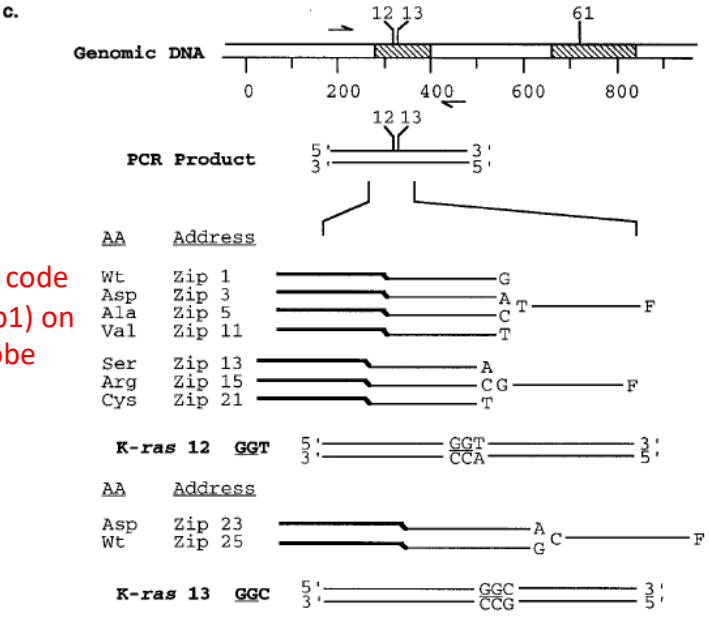
Keywords: zip-code addressing; DNA hybridization; thermostable DNA ligase; ligase detection reaction; single nucleotide polymorphism (SNP)



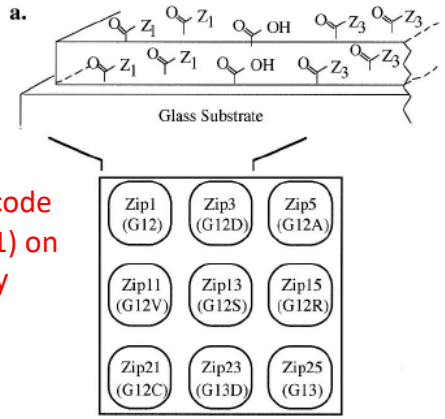
Complementary zip code (cZ1) on probe



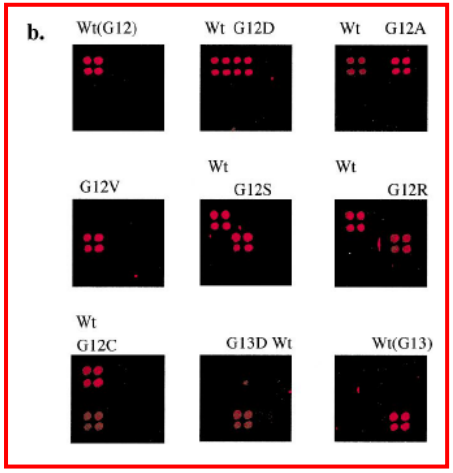
Zip code (Z1) on array



Zip code (Zip1) on probe



Zip code (Zip1) on array



Barany *et al.*, Filed Feb 9, 1996

(12) **United States Patent**
Barany et al.

(10) **Patent No.: US 7,083,917 B2**
(45) **Date of Patent: *Aug. 1, 2006**

(54) **DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING THE LIGASE DETECTION REACTION WITH ADDRESSABLE ARRAYS**

(75) Inventors: **Francis Barany**, New York, NY (US); **George Barany**, Falcon Heights, MN (US); **Robert P. Hammer**, Baton Rouge, LA (US); **Maria Kempe**, Minneapolis, MN (US); **Herman Blok**, Wemeldinge (NL); **Monib Zirvi**, New York, NY (US)

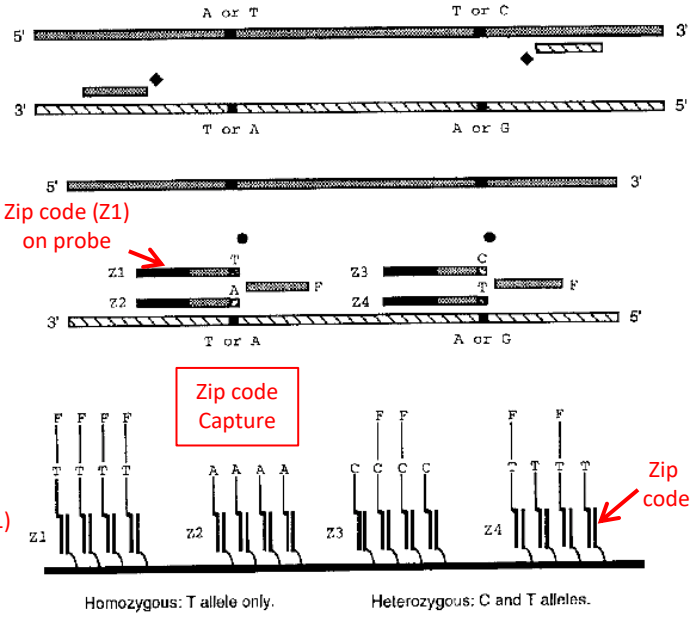
5,143,854	A	9/1992	Pirrung et al.
5,202,231	A	4/1993	Drmanac et al.
5,258,506	A	11/1993	Urdea et al.
5,278,298	A	1/1994	Chakraborty et al.
5,288,468	A	2/1994	Church et al.
5,290,925	A	3/1994	Fino
5,314,809	A	5/1994	Erlich et al.
5,324,633	A	6/1994	Fodor et al.
5,352,582	A	10/1994	Lichtenwalter et al.
5,371,241	A	12/1994	Brush et al.
5,391,480	A	2/1995	Davis et al.
5,405,783	A	4/1995	Pirrung et al.
5,407,798	A	4/1995	Martinelli et al.

PCR/ LDR

1. PCR amplify region(s) containing mutations using primers, dNTPs and *Taq* polymerase.◆

2. Perform LDR using allele-specific LDR primers and thermostable ligase.● Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.

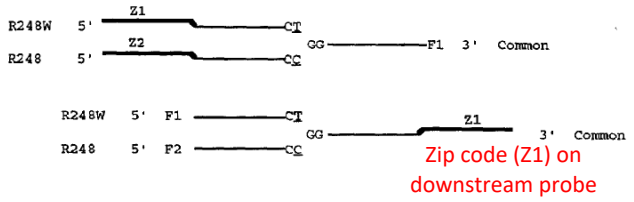
3. Capture fluorescent products on addressable array and quantify each allele.



Project 5 will develop solid-phase approaches for the simultaneous detection of LDR products. Products will be captured on a spatially addressable array, so that the position of a signal identifies a mutation. Each LDR product will have a "zip code" tail, which will be captured selectively by a "complementary zip code" on the solid support. Multiple reuse of a universal "complementary zip code" array is envisaged to allow detection of a wide range of cancers and genetic diseases.

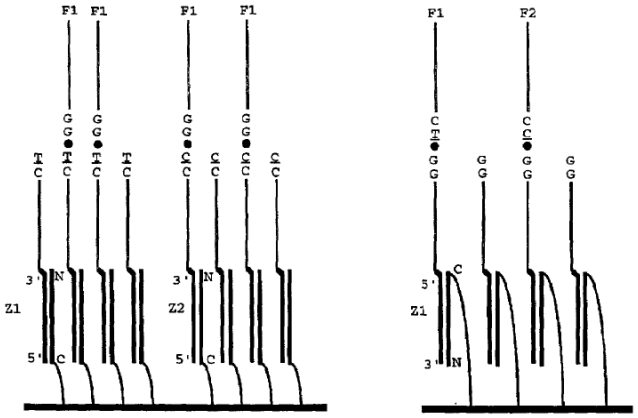
1994 NCI grant application had "zip code" tail on LDR product, and universal "complementary zip code" on the array.

Zip code (Z1) on upstream probe



Zip code (Z1) on downstream probe

Zip code (Z1) on Array



Zip code (Z11) on Array

TABLE 2

List of all 5 DNA/PNA oligonucleotide address sequences.

Zip #	Zip code	Sequence (5'→3' or NH_2 → COOH)	G + C
Zip11	1-4-3-6-6-1	TGCG-GGTA-CAGC-ACCT-ACCT-TGCG (SEQ. ID. No. 2)	15
Zip12	2-4-4-6-1-1	ATCG-GGTA-GGTA-ACCT-TGCG-TGCG (SEQ. ID. No. 3)	14
Zip13	3-4-5-6-2-1	CAGC-GGTA-GACC-ACCT-ATCG-TGCG (SEQ. ID. No. 4)	15
Zip14	4-4-6-6-3-1	GGTA-GGTA-ACCT-ACCT-CAGC-TGCG (SEQ. ID. No. 5)	14
Zip15	5-4-1-6-4-1	GACC-GGTA-TGCG-ACCT-GGTA-TGCG (SEQ. ID. No. 6)	15

Zip code (12, 14) on Array

TABLE 3

	Oligonucleotides used (5' to 3')
12	Aminolink- spacer 18- ATC GGG TAG GTA ACC TTG CGT GCG (SEQ. ID. No. 13)
14	Aminolink- spacer 18- GGT AGG TAA CCT ACC TCA GCT GCG (SEQ. ID. No. 14)
comp 12	CGC ACG CAA GGT TAC CTA CCC GAT (SEQ. ID. No. 15)
comp 14	CGC AGC TGA GGT AGG TTA CCT ACC (SEQ. ID. No. 16)

Complementary Zip code (comp 12, and comp 14) on Probe

Joint Development Agreement, November 9th, 1999

1.3. "Pre-Collaboration Illumina Intellectual Property" means all Intellectual Property Rights that are owned by, either partially or wholly, or licensed to, or otherwise controlled by, Illumina as of the Effective Date.

1.4. "Collaboration Illumina Intellectual Property" means all Intellectual Property Rights arising out of work performed under this Agreement that are conceived solely by one or more employees or agents of Illumina or its Affiliates.

6. **Intellectual Property; Patent Prosecution and Litigation; Licenses; Trademarks**

6.1. Ownership of Intellectual Property.

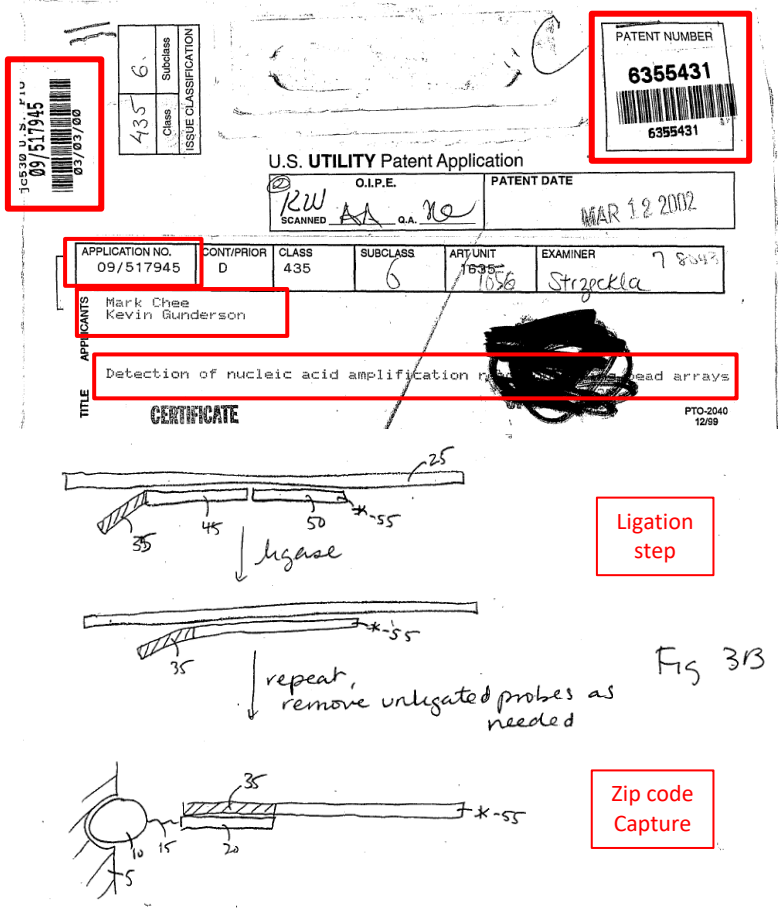
6.1.1. Pre-Collaboration Illumina Intellectual Property and Collaboration Illumina Intellectual Property. All rights and title to Pre-Collaboration Illumina Intellectual Property and Collaboration Illumina Intellectual Property, whether patentable or copyrightable or not, will belong to Illumina and will be subject to the terms and

6.2. Filing of Patent Applications.

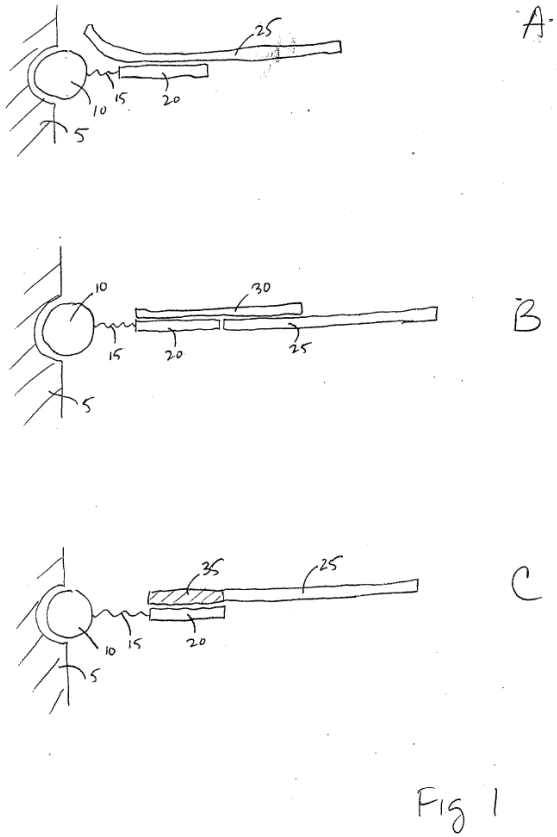
6.2.1. Collaboration Illumina Intellectual Property. Illumina will have the first right, using in-house or outside legal counsel selected by Illumina's sole discretion, to prepare, file, prosecute, maintain and extend patent applications for Collaboration Illumina Intellectual Property in countries of Illumina's choosing. Illumina will bear all costs relating to such activities. Illumina will solicit PEB's advice and review of the patent applications, and Illumina will take into consideration PEB's advice thereon. If Illumina elects not to

Illumina's intellectual property should have been reviewed by PE Biosystems. Thus, PE Biosystems was an "enabler" for Illumina, and did not notify the true inventors that their IP was being used or copied.

Zip code, cZip, Decoders, IllumaCode, IlluniCode, Capture Probe, Bead identifier, Adapter Sequence, Universal Tag Sequence



Figures 3A and 3B depict two preferred embodiments of OLA amplification. Figure 3A depicts a first ligation probe **45** and a second ligation probe **50** with a label **55**. Upon addition of the ligase, the probes are ligated. The reaction can be repeated and then the ligated primer is added to the array as above. Figure 3B depicts the same reaction but using adapter sequences.



Figures 1A, 1B and 1C depict three different embodiments for attaching a target sequence to an array. The solid support **5** has microsphere **10** with capture probe **20** linked via a linker **15**. Figure 1A depicts direct attachment; the capture probe **20** hybridizes to a first portion of the target sequence **25**. Figure 1B depicts the use of a capture extender probe **30** that has a first portion that hybridizes to the capture probe **20** and a second portion that hybridizes to a first domain of the target sequence **25**. Figure 1C shows the use of an adapter sequence **35**, that has been added to the target sequence, for example during an amplification reaction as outlined herein.

In these hastily drawn Illumina patent application figures, Illumina uses the terms “adapter sequence” and “capture probe” to describe Barany Lab’s zip code sequences.

Illumina submits provisional application 60/135,123 (K. Gunderson) on May 20, 1999:

A/PROV

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number EM193415915US. Date of Deposit May 20, 1999. I hereby certify that this paper or fee and listed enclosures is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231, on May 20, 1999

Typed or Printed Name: APRIL RICH

Signed:

Docket Number:	P-68088/DJB/RMS	Type a plus sign (+) inside this box → +

INVENTOR(S)/APPLICANT(S)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
GUNDERSON	Kevin		Encinitas, California

TITLE OF THE INVENTION (280 characters max)

ADDRESSING ARRAYS USING SEQUENCE SPECIFIC ADAPTERS

05/20/99 JC571 U.S. PTO

05/20/99 PTO 60/135123

ADDRESSING ARRAYS USING SEQUENCE SPECIFIC ADAPTERS

The present invention is directed to the use of "universal bead arrays" and methods thereof. A type of addressable array has been previously described, see WO 97/31256, hereby incorporated by reference in its entirety.

Barany Lab Patent

INVENTION DISCLOSURE FORM

1. **Name:** Kevin Gunderson, Mark Chee, John Stuelpnagel

2. **Date:** 5/10/1999

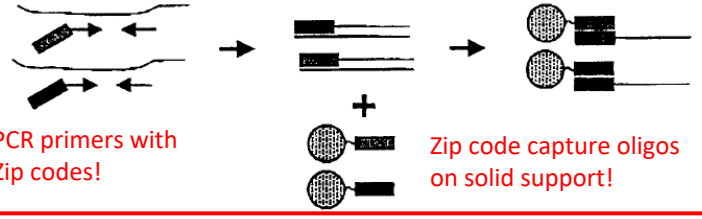
3. **Title of the Invention:** **Addressing an Array using Sequence-Specific Adapters**

4. **Describe the invention:** Use additional sheets if necessary. Attach descriptive materials such as drawings, sketches, photographs, etc. which may help illustrate the invention. Delineate new and important features. Make sure to include both the preferred embodiment as presently identified, and alternative constructions, procedures or equivalent components which can accomplish the same result as the preferred embodiment.

This invention disclosure describes the use of DNA adapters in conjunction with arrays comprising nucleic acids.

By attaching a specific hybridizing sequence, or "adapter" (e.g. DNA oligonucleotide) to a molecule of interest, and providing a complementary hybridizing sequence attached to a solid support (e.g. in a bead array format), the molecule of interest can be targeted specifically to the solid support. This provides a means of addressing a molecule of interest to a specific location. In the case of a randomly ordered array, the location, although specific, does not need to be known at the time of addressing. It can be determined after the fact, by decoding (as described previously in an Illumina patent application).

The adapter can be attached to the molecule of interest in a number of ways. If the molecule of interest is a nucleic acid sequence, the adapter can be incorporated by ligation, by chemical attachment, by synthesis, or other methods for joining nucleic acids. An example of incorporation by means of a PCR reaction is shown in Figure 1:



PCR primers with Zip codes!

Zip code capture oligos on solid support!

Figure 1. Incorporation of a nucleic acid adapter into a PCR product and subsequent targeting to a specific location. The adapter is chemically synthesized as part of a PCR primer. PCR reactions can be carried out singly or in multiplex format. The left panel shows 2 PCR reactions being carried out together, with each reaction labeled with a different adapter sequence (shown as grey and black rectangles). The center panel shows how the labeled PCR products can be mixed with solid supports carrying sequences complementary to the adapters. The right hand panel shows how each adapter binds to its complement, effectively targeting each PCR product to a separate location.

5. **State the primary purpose of the invention, including the need satisfied or problem solved by the invention:**

The invention allows a specified set of nucleic acid sequences to be used as "adapters" for many different assays, so that the assays, regardless of their composition, can be directed to specific locations and resolved from one another on an array comprising sequences complementary to the adapters.

6. **Prior art.** Include references, articles, talks, abstracts, patents, etc. which are relevant to either the state of the prior art or to the invention. Please include dates and provide copies whenever possible:

Chee, M. S. (1991) "Enzymatic multiplex DNA sequencing" Nucleic Acids Research **19**, 3301-3305 and refs therein.

Shoemaker, D. D. et al. (1998) Quantitative phenotypic analysis of yeast deletion mutants using a highly parallel molecular bar-coding strategy. Nature Genetics **14**, 450-456.

Illumina attempts to re-patent Barany Lab's universal arrays and zip code primers, by trying to rename them as "adapter".

Illumina's provisional application 60/135,123 (K. Gunderson) tries to re-patent Barany Lab's ideas from 3 years earlier.

Barany *et al.*, Filed Feb 9, 1996

(12) **United States Patent**
Barany et al.

(10) **Patent No.: US 7,083,917 B2**
(45) **Date of Patent: *Aug. 1, 2006**

(54) **DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING THE LIGASE DETECTION REACTION WITH ADDRESSABLE ARRAYS**

(75) Inventors: **Francis Barany**, New York, NY (US); **George Barany**, Falcon Heights, MN (US); **Robert P. Hammer**, Baton Rouge, LA (US); **Maria Kempe**, Minneapolis, MN (US); **Herman Blok**, Wemeldinge (NL); **Monib Zirvi**, New York, NY (US)

5,143,854	A	9/1992	Pirrung et al.
5,202,231	A	4/1993	Drmanac et al.
5,258,506	A	11/1993	Urdea et al.
5,278,298	A	1/1994	Chakraborty et al.
5,288,468	A	2/1994	Church et al.
5,290,925	A	3/1994	Fino
5,314,809	A	5/1994	Erlich et al.
5,324,633	A	6/1994	Fodor et al.
5,352,582	A	10/1994	Lichtenwalter et al.
5,371,241	A	12/1994	Brush et al.
5,391,480	A	2/1995	Davis et al.
5,405,783	A	4/1995	Pirrung et al.
5,407,798	A	4/1995	Martinelli et al.
5,412,087	A	5/1995	McGall et al.

PCR/ LDR

1. PCR amplify region(s) containing mutations using primers, dNTPs and *Taq* polymerase.
2. Perform LDR using allele-specific LDR primers and thermostable ligase. Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.
3. Capture fluorescent products on addressable array and quantify each allele.

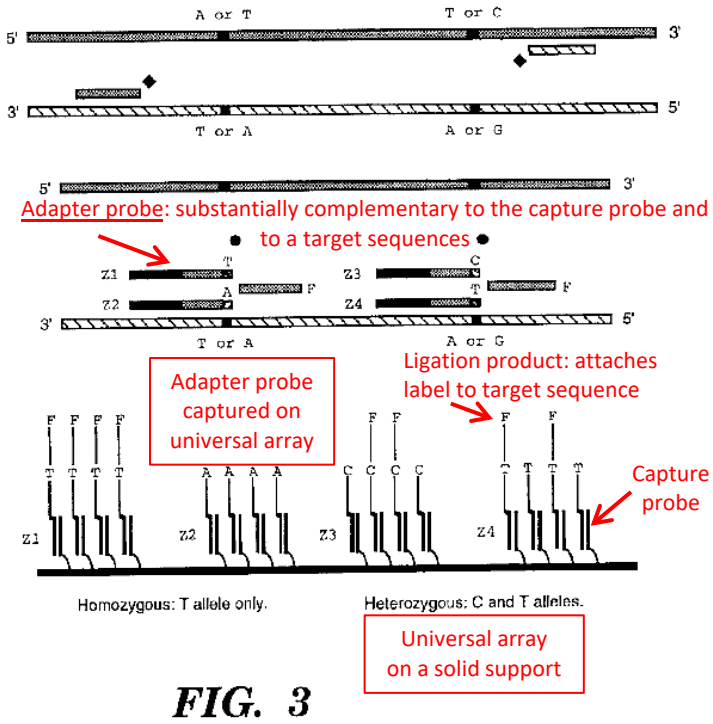


FIG. 3

Illumina, Filed May 20, 1999

A/PROV

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number EM193415915US. Date of Deposit May 20, 1999

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Typed or Printed Name: APRIL RICH

Signed:

05/20/99 JC571 U.S. PTO

Docket Number:	P-68088/DJB/RMS	Type a plus sign (+) inside this box → +

INVENTOR(S)/APPLICANT(S)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
GUNDERSON	Kevin		Encinitas, California

05/20/99 JC542 U.S. PTO 60/135,123

TITLE OF THE INVENTION (*280 characters max*)

ADDRESSING ARRAYS USING SEQUENCE SPECIFIC ADAPTERS

The present invention is directed to the use of "universal bead arrays" and methods thereof. A type of addressable array has been previously described, see WO 97/31256, hereby incorporated by reference in its entirety.

Barany Lab Patent

Generally, as is outlined in the attached invention disclosure, adapters can be made for bead arrays such are generally described in U.S.S.N.s 09/189,543; 08/944,850; 09/033,462; 09/287,573; 09/151,877; 09/187,289 and 09/256,943; and PCT applications US98/09163; US98/21193; US99/04473 and US98/05025, all of which are hereby incorporated by reference.

The microsphere array comprises subpopulations of microspheres that comprise capture probes that will hybridize to the adapter probes. The adapter probes generally comprise at least two parts; a first part that is substantially complementary to the capture probe on the bead, and a second part that is substantially complementary to a target sequence (although sandwich assays may also be done). Samples comprising target sequences are then added to the bead array, and detection proceeds via detection of a label directly or indirectly attached to the target sequence as an indication of the presence, absence or amount of the target sequence.

The methods of the invention find particular use in genotyping assays, i.e. the detection of particular nucleotides at specific positions.

Illumina substitutes the terms "adapter sequence" and "capture probe" instead of Barany Lab's term "zip code".

Illumina submits provisional application 60/135,123 (K. Gunderson) on May 20, 1999: Claims to be first to describe "Universal adapters", which is just another term for Barany LAb's "zip codes".

A/PROV

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

"EXPRESS MAIL" MAILING LABEL Number EM193415915US. Date of Deposit May 20, 1999

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Typed or Printed Name: APRIL RICE

Signed:

JC571 U.S. PTO 05/20/99

Docket Number:	P-68088/DJB/RMS	Type a plus sign (+) inside this box → +

JC542 U.S. PTO 60/135123 05/20/99

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
GUNDERSON	Kevin		Encinitas, California

TITLE OF THE INVENTION (*280 characters max*)

ADDRESSING ARRAYS USING SEQUENCE SPECIFIC ADAPTERS

7. Are there any publications, abstracts, submitted manuscripts, talks, etc. on this work (either already done or in the works)? Please provide details and dates:

None. But see related invention disclosure by Kevin Gunderson on use of oligonucleotide ligation with arrays.

8. Compare new and important features of the invention with the prior art, explaining why and how the invention is better:

With this invention, a master set of beads and decoder oligonucleotides can be reused many times. In the prior art, each assay would require the design and synthesis of a new set of capture sequences and decoders.

9. Please list known competitors or alternate technologies which solve the same problem:

None known.

10. Are there commercial products you envision? Please describe:

Libraries of beads comprising nucleic acid sequences; cognate libraries of labeled decoder nucleic acids; adapter sequences in electronic form; software for operating on adapter sequences (e.g. to design oligonucleotides incorporating adapter sequences); adapter sequences in physical form (e.g. "universal" adapters that can be attached to molecules of interest.

11. What are the immediate research plans or steps to be taken:

Research is ongoing. A set of 16 adapters is in use; set of 100 adapters will be prepared & tested in near future (Kevin Gunderson).

13. Earliest date and place invention was conceived, and substance of conception (identify people and records to support date and place, such as notebook numbers and pages):

Ask Kevin Gunderson re adapters & applications. "Universal adapters" first described here.

14. Name, title, signature, and address of each person who made an intellectual contribution to the invention described in this disclosure:

Kevin Gunderson 5/12/99

Mark Chee 5/12/99
155 15th Street, #24
Del Mar, CA 92014

John Stuelpnagel

15. Name and signature of two witnesses who are not inventors who understand the technical aspects of this invention:

Name Anthony W. Czarnik
Title CSO
Address 1101 Camino Arroyo
San Diego, CA

Todd A. Dickinson 5/12/99
3435 Lebon Dr. 1133
San Diego CA
92122

Illumina attempts to re-patent Barany Lab's universal arrays and zip code primers, shamelessly claiming ""Universal adapters" first described here".

4 years later, Illumina attempt to re-patent Barany Lab's '917 family patents.

60/180810 Provisional application filed by Jian-Bing Fan of Illumina, February 7, 2000

In order to make use of the array, the identity of the beads at each location must be determined. Illumina, Inc. has developed proprietary methods of rapidly and efficiently decoding an entire array which may contain up to 2,000 unique probe sequences. In order to make the technology available to researchers worldwide, Illumina has recently partnered with PE Biosystems to commercialize the BeadArray™ technology in combination with PE Biosystems' ZipCode™ chemistry. As shown in Figure 2, hybridization to the bead arrays is straightforward and has been demonstrated in Dr. Walt's laboratory at Tufts University and at Illumina.

The addressable array strategy:

To avoid the disadvantage of designing new arrays for each new set of targets, an alternative approach is to provide an array that is "universal" and can be used for any set of biological targets. This allows an investigator to use the same array for different target sequences, which removes the need for costly specialized designs. A universal array of this type has been described (Gerry et al., 1999). Such an array consists of a set of artificially generated probes that are sufficiently long and unique to hybridize with high specificity. These probes act as addresses or "zip-codes" on an array. In order to make use of the array, target sequences to be analyzed are linked with specific zip-code sequences (after PCR amplification, the complementary zip-code sequence will be used to hybridize to the zip-code probes on the array). Thus, any set of targets can be analyzed using the same set of zip-codes by attaching them to appropriate targets. This approach has been used for point mutation and SNP analysis (Gerry et al., 1999; Fan et al., 1999).

Fan, J-B. et al., (1999). Scaleable parallel genotyping using high-density oligonucleotide tag arrays. Manuscript in preparation.

Gerry, N. P., Witowski, N. E., Day, J., Hammer, R. P., Barany, G., & Barany, F. (1999). Universal DNA microarray method for multiplex detection of low abundance point mutations. *J Mol. Biol.* **292**:251-262.

Illumina admits – 4 years after Barany Lab's zip code patent was filed – that "in order to make use of the array, the identity of the bead at each location must be determined". Illumina admits that they use "PE Biosystems' ZipCode™ chemistry." Fu, who wrote the grant application admits the zip-code arrays were invented by Gerry-Barany, 1999, while Fan puts in a fake reference to claim the same year.

Illumina: Fan SBIR 1R43CA097851-01 Grant, submitted November 30, 2001

Form Approved Through 05/2004

7 9 0 8 0 7 Services

Grant Application 3 - 2001

Follow instructions carefully
Do not exceed 56-character length restrictions, including spaces

PI: FAN, JIAN-BING
1 R44 CA097851-01
Dual: HG,RR
IRG: ZRG1 SSS-Y(10) B

Council: 05/2002

Received: 12/03/2001

1. TITLE OF PROJECT
High-Throughput Methylation Profiling System

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)
Number: PHS 2001-2 Title: Phase I FAST-TRACK

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR	New Investigator ☐ No ☒ Yes
3a. NAME (Last, first, middle) Fan, Jian-Bing	3b. DEGREE(S) Ph.D
3c. POSITION TITLE Director, Genetic Analysis	3d. MAILING ADDRESS (Street, city, state, zip code) Illumina, Inc. 9885 Towne Centre Drive San Diego, CA 92121-1975
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Genomics	
3f. MAJOR SUBDIVISION Molecular Biology	

RESEARCH PLAN

A. SPECIFIC AIMS

This proposal aims to develop a robust and ultra high-throughput technology for simultaneously measuring methylation at many specific sites in a genome. The technology will be based on a bead-based array platform for genetic analysis. We have already used this platform to create a large scale single nucleotide polymorphism (SNP) genotyping system capable of generating more than a million genotypes per instrument per day. By adapting this system to detect and analyze methylation, we aim to provide a tool that will enable genome-wide methylation profiling in large populations. Methylation is involved in gene regulation and altered methylation patterns have been associated with various types of cancers (Baylin et al., 2001; Momparler and Bovenzi, 2000; Warnecke and Bestor, 2000). Therefore, the technology developed in this proposal will provide a powerful tool not only for fundamental genomic research, but also for cancer biology studies, with potential application to cancer classification and diagnosis, and anti-cancer drug target identification and drug screening.

Through a Zirvi FOIA request, the inventors learn that Illumina's J.B. Fan submitted a grant application to the NIH on November 30, 2001. In this funded application, Illumina boasts the ability to generate more than a million genotypes per instrument per day, but fraudulently conceal that they use the Barany Lab IP and trade secrets.

Illumina: Fan SBIR 1R43CA097851-01 Grant, submitted November 30, 2001

C.4.1 Genotyping Results

We are currently routinely multiplexing 96 SNPs per reaction (Fig. 7) and have also obtained good results with 384 multiplexes. DNA consumption is ~ 1 ng per genotype (100 ng in a 96-plex reaction), which is very efficient.

Principal Investigator Fan, Jian-Bing

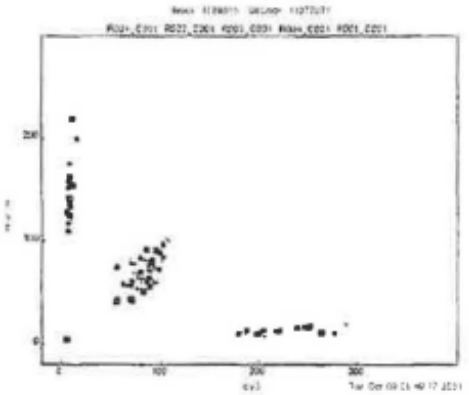

Figure 7. Example of a SNP assay from a 96-plex analysis on optical fiber bundle arrays in a 96-array matrix format. An additional 95 SNPs (not shown) were genotyped in the same reaction. The genotypes shown are for 96 samples processed in parallel in an array matrix. The intensity of allele "a" (labeled with Cy3) is plotted on the x-axis, and allele "b" (labeled with Cy5) is plotted on the y-axis. Each data point represents data from multiple beads in the array. As can be seen from the figure, all three genotypes are represented. The low intensity point near the origin is from a bad DNA sample. These results were generated using a high-throughput automated system in which robotic pipettors are used to carry out the assay procedures.

The system is accurate (~99%) and reproducible (~99%) at 96-plex, and currently generates more than half a million genotypes per day using a small number of array matrices.

Through a Zirvi FOIA request, the true inventors learn that Illumina's J.B. Fan grant application to the NIH on November 30, 2001, which literally infringes upon Barany Lab's '917, '470, and '293 patents using direct LDR-PCR with zip code array capture, shows "accurate" and "reproducible" results with multiplexing 96 SNPs per reaction, and claims good results with a 384 multiplex. This newly revealed information shows that contrary to Illumina's assertions, LDR-PCR works just fine without the need to do a "gap-LCR" step, and that the two are functionally equivalent.

Illumina: Fan SBIR 1R43CA097851-01 Grant, submitted November 30, 2001

Reading out methylation status. We will implement a methylation detection method using the SNP genotyping strategy shown above (Fig. 6). Non-methylated cytosines (C) will be converted to uracil (U) when treated with bisulphate. Uracil's hybridization behavior is similar to that of thymine (T). The detection of the methylation status of a particular cytosine can thus be carried out using a genotyping assay for a C/T polymorphism. Oligo-ligation assay probes can be designed such that one "ASO" is targeted to the "C" allele, i.e. the methylated one, while the other "ASO" is targeted to the "T", i.e. the non-methylated one (Fig. 6). The OLA-PCR assay procedures shown in Fig. 6 will be applied thereafter to determine the methylation status at the targeted sites. Each specific methylation site is interrogated with three oligos: C allele-specific, T allele-specific, and a downstream locus-specific oligo with an address sequence that uniquely corresponds to one specific bead type on the array. Standard protocols developed for SNP genotyping, such as the protocols for oligo annealing and ligation, PCR amplification, and array hybridization, can all be adapted for the methylation detection.

The experimental scheme described in this proposal is advantageous over other methylation detection methods in additional respects. (1) It allows oligos to hybridize directly with their genomic target regions, thereby omitting individual target-specific amplification. (2) The use of universal primers in PCR reaction reduces biased signal amplification, increasing the ability to multiplex the assay robustly and to provide quantitative measurements. The ability to amplify robustly also provides the potential to detect methylation with small numbers of cells, although that is not an aspect we plan to investigate in Phase I.

In addition, Illumina has partnered with Applied Biosystems to commercialize bead array systems for genotyping. Applied Biosystems will be responsible for worldwide sales, marketing and support of the collaboration systems, which are expected to be available in 2002.

Through a Zirvi FOIA request, the true inventors learn that Illumina's J.B. Fan grant application to the NIH on November 30, 2001, which literally infringes upon Barany Lab's '917, '470, and '293 patents using direct LDR-PCR with zip code array capture, was funded to do work invented by the Barany Lab. IIIlumina understood that Barany Lab's technology was "advantageous over other methylation detection methods" and cites the exact advantages that were articulated in Barany Lab's IP and trade secrets. Further, the grant highlights the Illumina and Applied Biosystems partnership, implying that Applied Biosystems was fully aware of this work, yet deliberately withheld Illumina's infringement to defraud the true inventors.

Illumina: Chee SBIR 1U54HG002753-01 Grant, submitted May 28, 2002

Form Approved Through 05/2004

PI: CHEE, MARK

1 U01 HG002753-01

Dual:

IRG: ZHG1 SRC(99)

Council: 08/2002

Received: 05/29/2002

Department of Health and Human Services

P 1 5 0 6 4 alth Services

Application

Do not exceed 56-character length restrictions, including spaces.

1. TITLE OF PROJECT

Highly Parallel SNP Genotyping for a Haplotype Map

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES

(If "Yes," state number and title)

Number: HG-02-005 Title: Large-Scale Genotyping for the Haplotype Map of the Human Genome

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR		New Investigator ☒ No ☐ Yes
3a. NAME (Last, first, middle) Chee, Mark Stephen		3b. DEGREE(S) PhD
3c. POSITION TITLE Vice President, Genomics		3d. MAILING ADDRESS (Street, city, state, zip code) 9885 Towne Centre Drive San Diego CA 92121-1975
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION Molecular Biology		
3g. TELEPHONE AND FAX (Area code, number and extension) TEL: (858) 202-4503	FAX: (858) 202-4680	E-MAIL ADDRESS:mchee@illumina.com

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt ☐ No ☒ Yes If "Yes," Exemption No. 4	5. VERTEBRATE ANIMALS ☒ No ☐ Yes	
☐ No ☒ Yes	4b. Human Subjects Assurance No.	4c. NIH-defined Phase III Clinical Trial ☐ No ☐ Yes	5a. If "Yes," IACUC approval Date	5b. Animal welfare assurance no

6. DATES OF PROPOSED PERIOD OF SUPPORT (month, day, year—MM/DD/YY)		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
9/20/2002	9/19/2004	$7,072,747	$7,310,685	$14,879,437	$15,355,660

Through a Zirvi FOIA request, the true inventors learn that Illumina's Mark Chee fraudulently submitted a grant application to the NIH on May 28th, 2002, which was subsequently funded for $15,355,660. Thus, the true inventors learn for the first time that Illumina was paid over $15 million by the NIH to develop highly parallel SNP genotyping based on Barany Lab's LDR-PCR technology as covered in Barany Lab's '917 patent filed Feb 9, 1996, Barany Lab's '470 patent filed May 29, 1996, and Barany Lab's '293 patent filed Jan 6, 1999.

Illumina: Chee SBIR 1U54HG002753-01 Grant, submitted May 28, 2002

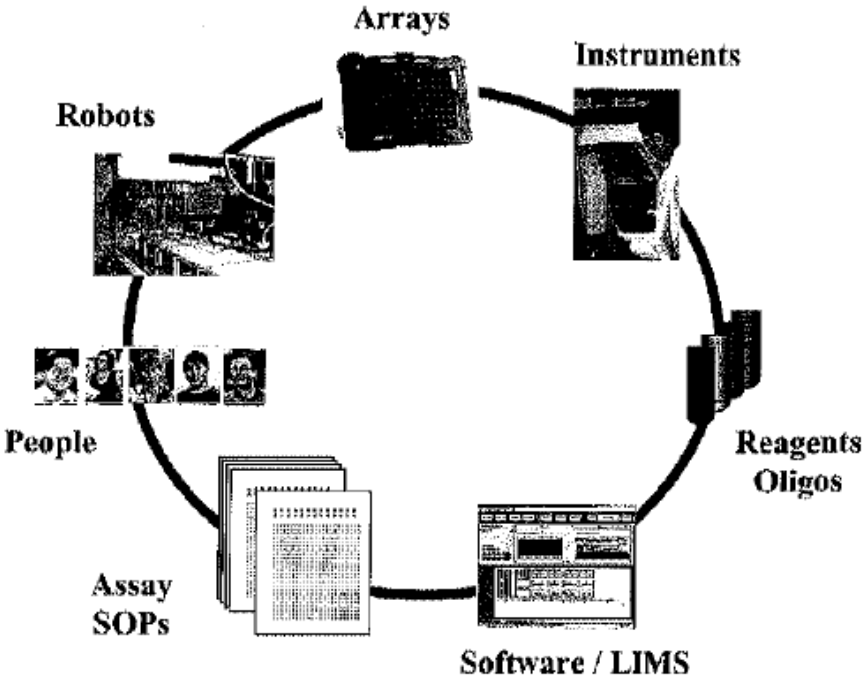

Figure 1. Informatically integrated high-throughput genotyping system based on BeadArray technology. The system is modular, and integrated using barcode reading and LIMS supervision. Miniaturization is achieved by using a fiber-optic bundle as a substrate for the highest-density microarray available today. Ninety-six of these arrays are held together in a matrix (Array of Arrays™ matrix) that matches the spacing of a standard 96-well microplate. In order to use efficiently the high capacity of the platform, the SNP assays developed at Illumina have been designed for a high level of multiplexing. Currently, Illumina's production genotyping system routinely multiplexes 288 SNP assays in each well of a microplate, and we have recently achieved excellent results with 1,152-plex assays.

Through a Zirvi FOIA request, the true inventors learn that Illumina's Mark Chee fraudulently submitted a grant application to the NIH on May 28th, 2002, that is completely based on Barany Lab's LDR-PCR technology as covered in Barany Lab's '917 patent filed Feb 9, 1996, Barany Lab's '470 patent filed May 29, 1996, and Barany Lab's '293 patent filed Jan 6, 1999. The entire integrated system is completely dependent on Barany Lab's zip code arrays and LDR-PCR reactions, without these critical components, the system would not exist.

Illumina: Chee SBIR 1U54HG002753-01 Grant, submitted May 28, 2002

C.4 Multiplexing

By using objective measures of quality described above, we have optimized assay procedures to increase multiplexing levels from 48-plex to 1,152-plex within a period of about 12 months (Fig. 3). Since

Proprietary Info

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