Avatar DNA Nanohybrid System in Chip-on-a-Phone

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Long admired for informational role and recognition function in multidisciplinary science, DNA nanohybrids have been emerging as ideal materials for molecular nanotechnology and genetic information code. Here, we designed an optical machine-readable DNA icon on microarray, Avatar DNA, for automatic identification and data capture such as Quick Response and ColorZip codes. Avatar icon is made of telepathic DNA-DNA hybrids inscribed on chips, which can be identified by camera of smartphone with application software. Information encoded in base-sequences can be accessed by connecting an off-line icon to an on-line web-server network to provide message, index, or URL from database library. Avatar DNA is then converged with nano-bio-info-cogno science: each building block stands for inorganic nanosheets, nucleotides, digits, and pixels. This convergence could address item-level identification that strengthens supply-chain security for drug counterfeits. It can, therefore, provide molecular-level vision through mobile network to coordinate and integrate data management channels for visual detection and recording.

In 1996, Joe Davis created the first biological analog icon, called Microvenus, using recombinant DNA techniques to represent artistic information1,2. This insight into genetic art has challenged multidisciplinary scientists to develop digital-writing strategies and rapid-reading techniques of DNA language for next-generation data storage3–10. The lifespan of these devices are much greater than those of devices based on magnetic, electronic, or photonic phenomena11–13.

We describe the Avatar DNA that identifies DNA information using chip-on-a-phone, and convergence of this system with nano-bio-info-cogno (NBIC) technology for safe supply-chain management. Avatar DNA is an optical machine-readable hybrid icon fabricated on a biosensor through combination of biological DNA code with digital automatic identification and data capture (AIDC) image code, and therefore, it can connects specific information encoded in DNA base-sequence from an off-line AIDC image code to an on-line mobile computer system likes smartphone. Fig. 1 and Fig. S1 show how the digital DNA icons inscribed on a microarray chip can be automatically captured with a mobile phone camera, and how the information can be directly accessed by software. This technology employs fabricated DNA image codes for AIDC to rapidly transmit information to remote databases, including text messages, base-sequences, indexes, profiles, documents, and URLs.

Results

We successfully identified the DNA-AIDC hybrid icons using a smartphone in a laboratory environment. Two different AIDC image codes such as two-dimensional (2D) Quick Response (QR) and three-dimensional (3D) ColorZip were fabricated in spot-arrayed DNA chips, respectively. As shown in Fig. 2, the Avatar hybrid icons of biological DNA and digital AIDC image designed here are geometrically identical to the typical QR code and ColorZip code. Unique information can be represented in the DNA-AIDC hybrid icons through specific combination of DNA base-sequences and AIDC image patterns. In the each spot of microarray chips, different probe DNA with a specific base sequence are embedded to telepathically capture complementary target DNA code labelled with specific fluorophores. The fluorescently labelled DNA encoded functions as a photographic information emulsion. When these Avatar DNA icons were acquired by smartphone with application software, the DNA-QR icon was directly coupled with the text information of Avatar DNA, and the DNA-ColorZip icon was also linked to the information in the form of index including name card, definition, three different base-sequences, and website address.

The first model icon contained 21-by-21 modules with red-fluorescence dots arranged in a square grid on a white background (Fig. 2A). The DNA base-sequence was stored in a single DNA-QR code by automatically assigning binary number values to a 2D matrix through a logical QR code algorithm14. In our experiment, the icon...
in the form of Version 1 was simultaneously recognized as a QR code matrix of square dots mapped by binary digits of ones (red modules are perceived as black) and zeros (white background). The mobile reader likes smartphone simultaneously scanned the Avatar DNA-QR icon on the DNA chip by detecting its structural patterns, including position, module, and data area. The Avatar DNA information was then decoded through the sequence of black (B) and white (W) modules on a certain line, 1:0:1:1:0:1 (B:W:B:B:W:B), that passes the center of the detector from an omnidirectional angle. This could enable ultra-high-speed reading of the Avatar DNA QR code with the mobile chip-on-a-phone.

The second model icon contained a 25-subset array of 4-by-4 dots emitting 4 different colors (red, green, blue, and black) with a total of 20-by-20 modules (Fig. 2B). This icon was also able to be scanned as a ColorZip matrix that was mapped by color-filled 5-by-5 square cells. The 2-bit data can be expressed by one color cell, since each cell in the ColorZip code was encoded with one of four colors. Therefore, if the colors of the data cells D11, D12, D22, and D24 are encoded as red, green, black, and blue, the values are decoded as 10, 01, 11, and 00, respectively, according to the ColorZip code theory (International Standard ISO/IEC 18004:2006 Information technology — Automatic identification and data capture techniques — QR Code 2005 bar code symbology specification)\(^{15}\). In our experiment, the smartphone decoder used sampled pixels from each cell, and classified the colors of sampled pixels from the DNA chip into bit-stream data.

These results can be explained by fact that whole spots of DNA chip, namely, 226 spots for the QR chip or 320 spots for the ColorZip chip, can be recognized as a single digital image code icon consisted of DNA pixels, DNA-QR code icon (226 pixels) and DNA-ColorZip code icon (320 pixels), respectively. It is worthy of note that, therefore, the Avatar DNA icon can be sufficiently identified with real DNA molecules at concentration of less than nanomolar-level (10\(^{-9}\) moles) through mobile phone camera, since DNA molecules...
counterfeiting incidents of Avastin, an injectable cancer medicine, highlighted the vulnerabilities in U.S. distribution chains for purchases of non-FDA-approved or unregulated drugs from a foreign supplier\(^4\). The counterfeit versions can occur anywhere along the chain, including the manufacturer, distributor, and supplier. These problems present significant risks to public health. It is important that inspection agencies improve supply-chain security and reevaluate current safety strategies within the global pharmaceutical market.

**Discussion**

The DNA-AIDC hybrid platform described here is a new infohybrid discipline that combines information technology and hybrid science, which can provide strong systems approach to supply-chain safety and security issue through comprehensive item-level identification based on a DNA molecule. Our approach involves NBIC convergence, where the main building blocks are interactive between boundaries with Avatar DNA. In a similar principle of NBIC convergence system defined from U.S. National Science Foundation\(^25\), our NBIC convergence is stands for:

- **Nanotechnology from nanosheets**: Inorganic nanoparticles in the form of exfoliated metal hydroxide nanosheets with a chemical composition of \([M^{2+},M^{3+},(OH)_2]^{n+}\) (where \(M^{2+}\) = divalent metal cations; \(M^{3+}\) = trivalent metal cations; \(0.2 \leq \text{molar fraction of } x \leq 0.33\)) that originate from the 2D layered compounds with macromolecular anisotropic properties\(^{26-27}\). The ultrathin nanosheets have a thickness of \(~1\) nanometer, with a lateral size of several tens of nanometers. Nanosheets can be used for supramolecular hybrid assembly with functional substances like a DNA molecule at the molecular level to control cognitive responses to external stimuli.

- **Biotechnology from nucleotides**: Rationally designed and fabricated DNA molecules consist of four digital nucleotides (A/T/C/G) with functional labels\(^{28-29}\). Lab-on-a-chip technology enables molecular sensing to read information stored in DNA and transmit the information for identification and communication\(^{30-32}\).

- **Information technology from digits**: An applied computer system for software and hardware, including a digit algorithm and a mobile device that can interpret DNA information with logical data processing (encoding-encrypting-decrypting-decoding), is linked with wireless networking and tele-info communication.

- **Cognitive science from pixels**: A cognitive process co-evolved with infocommunications using artificial intelligence and a smartphone equipped with an automatically focusing optical camera. This recognizes and acquires digital information images using a similar principle to that of the optic nervous system of the human eye.

The Avatar DNA chip platform addresses the counterfeit incidents involving Avastin, an injectable cancer medicine. This technology is a practical application that strengthens security for supply-chain safety through a comprehensive item-level identification system. Proof-of-concept experiments were performed with a systems approach involving four primary steps: encoding, encrypting, decrypting, and decoding (Fig. 3).

The encoding step created phenotype DNA-AIDC icons that contained information about Avastin encoded in a specific DNA sequence (Fig. 3A). The integrity mark ‘AVASTIN DNA’ was encoded with DNA *in silico*, and then the information was expressed as a QR or ColorZip code. The ‘AVASTIN DNA’ binary code contains 88 digits with 11 bytes represented via ASCII characters, ‘01000001 01010110 01000001 01010011 01010010 01001001 01001110 00100000 01000100 01001110 01000001’. Using the base-3 (0/1/2) Huffman-compression coding method, the corresponding characters were converted to 55 trits, ‘02022 22102 02202 12210 20112 02101 10220 02212 21001 01220 02022’. Using a practical
DNA encoding method, the secured ‘AVASTIN DNA’ code would be stored in the form of cyber DNA with 55 non-repeated base-sequences, ‘CACAT GCTAT ATATG ATGAC ACTCA CAGTC TATGT ATGAT GACGA GTGCG TGTGC’. This drug-integrity information was then displayed with mobile phone-recognizable image matrixes, including QR code (Version 9 with 53-by-53 modules) and ColorZip code (5-by-5 cells). When these DNA-AIDC models were generated, a 6-digit numeric batch number (20130101) and expiration date (JAN 2013) were included according to FDA-approved packaging for Avastin.

The encrypting step encapsulated artificial DNA molecules conjugated with red, green, and blue color fluorophores inside a supra-molecular inorganic nanobody (DNA@Nano), and placed them behind the generated AIDC patterns in the printed form of a packaging label to be affixed onto the drug vials (Fig. 3B). A naked DNA molecule is easily destroyed in unfavorable environmental conditions, and synthetic DNA molecules should be protected within adequate hosts. Inorganic nanoscale structures were superior to biological hosts such as microorganisms, because biological hosts may induce mutations or damage to the embedded DNA. Therefore,}

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**Figure 3 | Avatar DNA systems approach with NBIC convergence during proof-of-concept workflow on drug integrity and supply-chain security.** (A) Encoding generates the AVASTIN DNA-AIDC hybrid icons: the QR code, ColorZip code, and their corresponding DNA molecules are prepared to carry the information of AVASTIN drug. (B) Encrypting prints the DNA-AIDC hybrid tags: the fluorescence- and sequence-encoded DNA molecules with a size of 100 nm are encapsulated inside spherical nanocavity with a wall thickness of 10 nm reassembled with metal hydroxides nanosheets to form a DNA@Nano core-shell structure. Thus stabilized biological DNA is ink-jet printed safely from severe chemical resistant so that the dually coded DNA-AIDC hybrid tags are transmitted to a receiver. (C) Decrypting reads the fluorescent DNA-AIDC hybrid tags: after scanning the DNA-AIDC tags under fluorescence illumination, and then the resulting fluorescent DNA-AIDC images are recognized by smartphone camera with application software to read the pre-encoded information of AVASTIN drug (Inset face image was authorized by Yong-Gun Shul at Yonsei University, Republic of Korea). (D) Decoding identifies the DNA-AIDC hybrid icons: following hybridization experiment for detecting DNA within 1 second time at a concentration of 100 picomole, the resulting Avatar DNA icons on chip are fluorescently imaged by scanner, and then On/Off identified by smartphone readout.
we encapsulated each DNA molecule in the duplex form of 35 bases conjugated with different fluorophores (100 nm in diameter) into a spherical inorganic nanoshell with a wall thickness of 10 nm. This inorganic shell was a hermetic diffusion barrier that protected the supramolecular assembly and the DNA molecule from endonucleases, oxidative stress induced by free radicals, and high-temperature in a colloidal suspension (see the supplementary information). Therefore, the artificial DNA stabilized inside the robust nanobody could be used to encode the ‘AVASTIN DNA’ security mark, which could be printed with the desired AIDC labels onto a piece of transparent adhesive paper. The DNA-QR code pattern was produced with one kind of DNA@Nano diluted with a black water-based ink, and used 100 ppm DNA. The DNA-ColorZip code matrix was printed with a series of three different kinds of DNA@Nano diluted with an aqueous solution at the DNA concentration of 100 ppm containing polymeric wetting agent.

The decrypting step performed capture and reading of AVASTIN DNA-AIDC images based on a smartphone reader at authentication nodes for timely oversight (Fig. 3C). If this DNA-AIDC was packaged as part of FDA-approved labeling into all legitimate products, they could be effectively tracked and traced to monitor sales records and protect against counterfeiting. We obtained proof-of-principle by automatically reading scanned fluorescent images for both DNA-QR and DNA-ColorZip codes using a smartphone camera and a conventional application, typically achieved in a non-destructive manner. The scan displays the hidden drug-integrity DNA code on the screen of the smartphone. The fluorescent AIDC images also serve as sentinels to tag a specific index of secured DNA information (similar to the file header in magnetic tape) for later retrieval and identification. The off-line DNA-AIDC tag can retrieve authentic information by directly connecting to an on-line database library linked to the URL of the Office of Drug Security, Integrity, and recalls of the U.S. FDA, to browse and cross-check drug integrity counterfeits.

Methods

Avatar DNA-AIDC hybrid icon. Capture (Probe) DNA with 50 base-sequences were prepared from Integrated DNA Technologies, USA. One capture DNA [A] was used for the DNA-QR code. Three different capture DNA were used for the DNA-ColorZip code as follows: (1) capture DNA [A] (5′-NH2-TTT TTT TTT GCC GCC ACC CAC ACC ACC AGA ATG ATG GCC GTC ATG TC-3′); (2) capture DNA [B] (5′-NH2-TTT TTT TTT TTT GAG TAC TAT AAA ATT AAT TTG GCC GAC CTT TG GG TCC-3′); and (3) capture DNA [C] (5′-NH2-TTT TTT TTT TTT GTC ACC ACA TCA AAG AAG ATT TCC ATT TAC CC-3′). The Avatar DNA chips were custom-fabricated by Genomicity Inc., Korea. In the DNA-QR code, there were 228 spots within 21 × 21 arrays per block (4 mm × 4 mm = 16 mm² area), and the spot diameter was 140 µm with 40-µm pitch between spots. In the DNA-ColorZip code, there were 320 spots within 20 × 20 arrays per block (4.5 mm × 4.5 mm = 20.25 mm² area), and the spot diameter was 140 µm with 80-µm pitch between spots. As-prepared capture DNA were spotted using an Omnicrator® Microarrayer (GeneMachines, San Carlos, CA) onto silanized glass slides. The fluorprobe-labeled target DNAs with 35 complementary base-sequences were synthesized by Integrated DNA Technologies. One red-color target DNA, [A′-Cy5], was used in the DNA-QR code. The following three different target DNAs were used in color target DNA, [A′-Cy5] hybrid code icon: 1) red-color target DNA, [A′-Cy5] (5′-Cy5-ATT GGG AGG CTC ATT CTG GTG TGG CGT CGG CC-3′); 2) green-color target DNA, [B′-Cy3] (5′-Cy3-GAC AAC AGG TCC GCC ACT TTA ATT TTA TAG ATC TC-3′); and 3) blue-color target DNA, [C′-Alexa350] (5′-Alexa350-GTA TAA ATT GGA AAA ATC TTC TGT GTC ATG AC-3′). All target DNA samples (10 nM) were suspended in 80 µl of hybridization buffer (10% dextran sulfate, 0.3% SDS, 30% formamide). The hybridization mixtures were directly introduced to each Avatar DNA chip. After incubating at 42 °C for 30 min, thus hybridized chips were washed with gentle agitation to eliminate non-specific binding as follows: 5 min at 42 °C in 2 × SSC and 0.1% SDS, 5 min at room temperature in 0.1 × SSC; and 5 min at room temperature in 0.1 × SSC, (twice). The Avatar DNA icon images were visualized with a fluorescencer scanner (Typhoon 9400, Amersham Biosciences Inc., USA) with software (Typhoon scanner control) at appropriate sensitivity levels of the photomultiplier (PMT), at 488 nm for Alexa 350, 532 nm for Cy3, and 633 nm for Cy5. The results were analyzed by ImageQuant software. After acquisition chip images by scanner instrument, the chip data images were then recognized and captured by smartphone (iPhone touch 5th generation, Apple Inc., USA) using either QR code application (ELECOM QR Code Reader) or a ColorZip code application (COLORCODE® V3.0). The distance between the fluorescence images and the smartphone reader was approximately 20 cm using a typical light source in a laboratory environment. Finally, thus decoded images from the Avatar DNA icon chip were directly captured on the smartphone screen for figure display.

Avatar DNA NBIC convergence system for drug supply chain management. In the encoding step, the secured text ‘AVASTIN DNA’ was encoded with a DNA base-sequence in silico, and information was then generated in the format of a QR code or ColorZip code. The 11 characters (including one space) of ‘AVASTIN DNA’ were represented as the binary code via ASCII characters. Using the base-3 (0/1/2) Huffman-compression coding method, the 88 bits of characters were then converted into the ASCII characters using the Huffman coding step, the secured text ‘AVASTIN DNA’ was encoded with a DNA base-sequence, and information was then generated in the format of a QR code or ColorZip code. The Avatar DNA icon images were visualized with a fluorescencer scanner (Typhoon 9400, Amersham Biosciences Inc., USA) with software (Typhoon scanner control) at appropriate sensitivity levels of the photomultiplexer (PMT), at 488 nm for Alexa 350, 532 nm for Cy3, and 633 nm for Cy5. The results were analyzed by ImageQuant software. After acquisition chip images by scanner instrument, the chip data images were then recognized and captured by smartphone (iPhone touch 5th generation, Apple Inc., USA) using either QR code application (ELECOM QR Code Reader) or a ColorZip code application (COLORCODE® V3.0). The distance between the fluorescence images and the smartphone reader was approximately 20 cm using a typical light source in a laboratory environment. Finally, thus decoded images from the Avatar DNA icon chip were directly captured on the smartphone screen for figure display.

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ink solution (pH 7.2) squeezed from the original cartridge (No. 98) in an HP Deskjet printer. For the AVASTIN DNA ColorZip code, ink-free aqueous solutions of each DNA@Nano, at a DNA weight content of 100 ppm, were made with 0.4% (w/v) of Surlyn 440 surfactant (Air Products), which was necessary for reliable printing. A 10-ml solution of each DNA@Nano was then loaded into a blank inkjet cartridge compatible with the desktop inkjet printer. Once printed, the labels were dried for 10 min at room temperature.

In the decrypting step, the fluorescence of the AVASTIN DNA code was visualized using a fluorescence scanner set for 488 nm for Alexa350, 532 nm for Cy5, and 633 nm for Cy5 using appropriate PMT sensitivity levels. The results were analyzed with ImageQuant software. Thus obtained fluorescent images were then recognized using either a QR-code application (ELECOM QR Code Reader) or a ColorZip-code application (COLORCODE V1.0) downloaded on a smartphone (iPhone touch 5th generation, Apple Inc., USA), and finally were captured for data display.

In the decoding step, the DNA from DNA@Nano was collected by thawing and dissolving the LDH matrix from the printed code labels. The DNA in the LDH nanoshell was then released by dissolving LDH in a slightly acidic solution at pH 4 along with the addition of ethylenediaminetetraacetic acid disodium salt (EDTA) for 15 min at ambient temperature. Each collected DNA hybridization mixture was then directly detected with the corresponding Avatar DNA-chip using typical protocols. Finally, Avatar DNA-chips were read by smartphone and captured to display their information on screen.

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Author contributions
D.H.P. designed the original idea and performed experiments and wrote the manuscript. C.J.H. partly assisted experiments. Y.G.S. contributed to the discussion and important insights. I.H.C. conceived the original idea, supervised the whole study, and made critical comments on the manuscript.

Additional information
Supplementary information accompanies this paper at http://www.nature.com/srep/