OH_2 Laboratories

Re-engineering Drug Discovery

Company Overview

February 2015

David Levy, Ph.D.
General Manager and Chairman
[redacted]

Introductions:

The OH_2 Laboratories Team

Board of Managers

David Levy, Ph.D.
Chairman and General Manager, OH2
Founder, Digit Wireless, LLC
Founder, TH, Inc
Design Engineer, Apple

Marc Rioult, Ph.D
Managing Director, 3DMatrix
Senior Licensing Officer, MIT TLO

Kevin Munnelly, Ph.D.
President & CEO, Gen9
GM, Life Technologies,
VP and GM, BioTrove

Steve Yang, Ph.D.
Director, Sentilaia
Consultant, McKinsey

Scientific Advisory Board

Shuguang, Zhang, Ph.D.
Lab Head, MIT
170 publication
36 patents and pending patents
Founder, 3D Matrix
Many awards

Robert Langer, D.Sci.
David H. Koch Institute Professor , MIT
1,250 Publications
1,050 patents
Many awards
Many, many Companies

Alex Rich, M.D.
Professor of Biophysics, MIT
550 Publications
Many awards

David Jin, M.D.
Practicing Oncologist and Researcher
2012 Top Chief Medical Officer in America
2014 Leading Physicians in the World

Significance of Our Work

About 50% of medications function by GCPR signaling.
99% of them were “lucky”: They worked prior to science understanding GPCRs.

Imagine if we could now target-design medications to signal through specific GPCR receptors...

What We Do

We produce GPCR^{QTY}, mAb^{QTY}, and Receptor^{QTY} :
synthetic materials created with our patented algorithms
to target-design stable water-soluble variants of any
desired protein, especially membrane proteins, while
maintaining the functionality of the original.

The result is a foundational technology:
a fundamental tool that opens many doors.

Monetization

The ability to produce stable water-soluble versions of proteins that are naturally insoluble brings value to several areas:

- Drug Discovery
- Research Tools
- Diagnostics
- mAB-Similar Products
- Autoimmune/Allergy Therapy
- Viral Therapeutics
- Molecular Sensors

OH2 is a holding company, ultimately intending to form subsidiaries to monetize each.

Drug Discovery

GPCR^{QTY} provides a critical revitalization of drying pharma pipelines:

- Addresses compounds with poor solubility (over 40% of drugs) offering increased efficacy and faster, cheaper development.
- Enables novel drug candidates for GPCR-mediated diseases:

Prostate cancer (GPR68/OGR1)	Breast Cancer (CXCR4)	Lung cancer (GPR87)
Cancer metastasis (CXCR4)	Parkinson's (GPCR 37)	Alzheimer's (GPR3)
Leukemia (P2Y8/P2 R Y8)	Asthma (CCR3.CXCR2)	Arteriosclerosis (GPRS 176)
Bipolar disorder (GPRS 78)	Ovarian Cancer (OGR1)	Colon cancer (MAS1)
Osteoarthritis (GPR22)	Autism (GPCR 63)	Diabetes (GPCR 21)

(Plus over 700 others and the list grows almost daily.)

Research Tools

Providing GPCR^{QTY}, mAb^{QTY}, and Receptor^{QTY} products to research laboratories, enables others to explore the benefits of water-soluble proteins.

Diagnostics

GPCR^{QTY} materials maintains ligand binding ability to specific antigens/receptors is a low-cost and stable medium enabling a new class of novel, low-cost diagnostics.

mAB-Similar Products

mAb^{QTY} offers new molecular therapeutics:

- Target-designed to be similar to monoclonal antibodies, but easier to produce.
- Engineered to reduce mAb aggregation and increase long-term storage.

Autoimmune/Allergy Therapy

GPCR^{QTY} can be used as a decoy therapy (similar to Enbrel/Etanercept).

This approach can theoretically be used for any disease or condition associated with GPCR signaling.

Viral Therapeutics

Receptors^{QTY} can be use to trap viruses including: HIV, Ebola, Marburg & Lassa - for rapid reduction of viral loads.

Molecular Sensors

Due to their stability, low-cost and high degree of molecular selectivity, Receptors^{QTY} can be used to create ultra-sensitive bionic detectors. (e.g. a chip-based bionic nose.)

The Science -

Using CXCR4 as an example

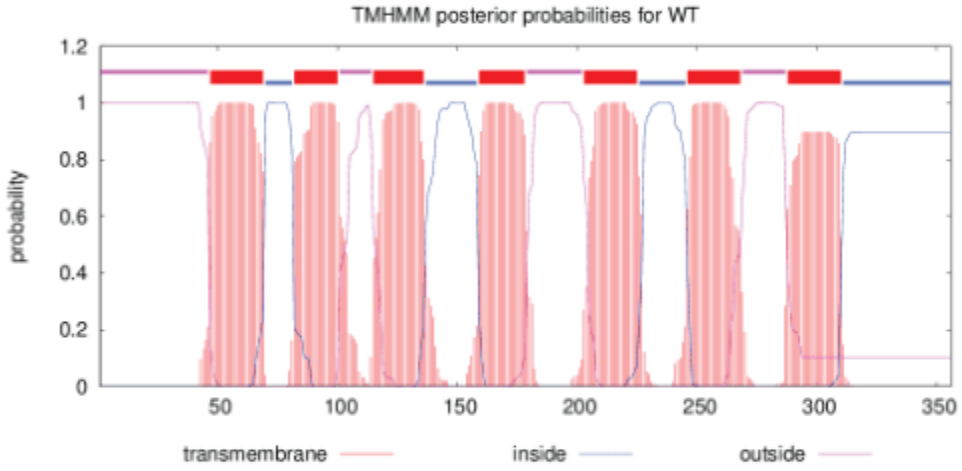
The following 7 slides explains how we can produce $CXCR4^{QTY}$, a functional soluble CXCR4 variant.

- Re-Coding CXCR4
- Comparing Structures
- Comparing Solubility
- Thermal Stability
- Circular dichroism Spectra
- Natural SDF1 ligand Binding
- X-Ray Diffraction

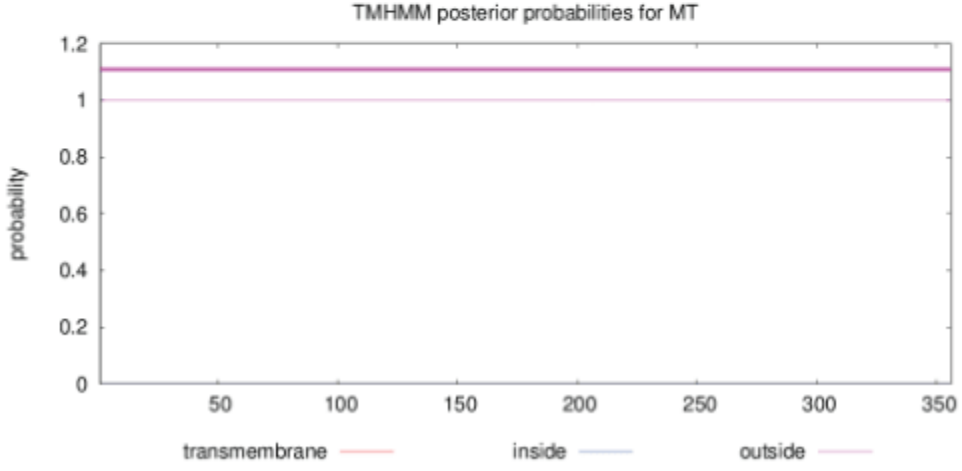
The variant structure was target-designed, not by trial and error.

Coding CXCR4^{QTY} from CXCR4

7 distinctive Trans membrane helices

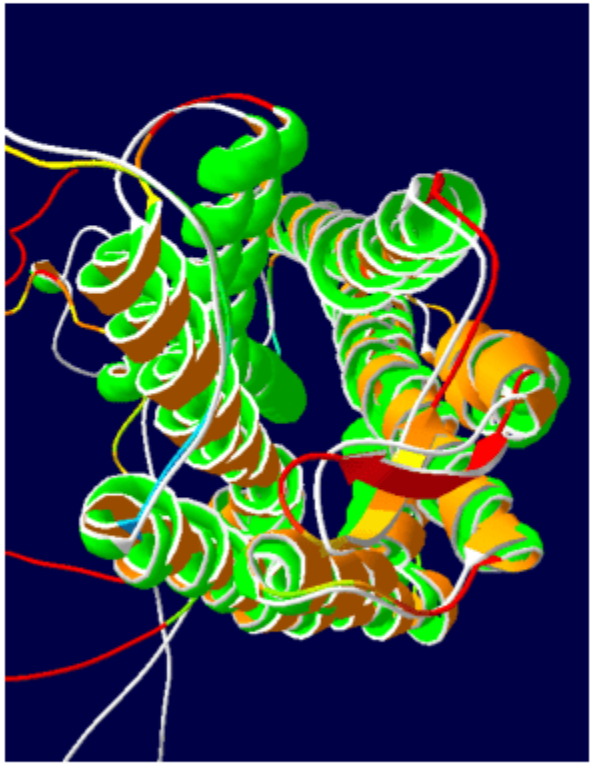


0 Trans membrane helices!

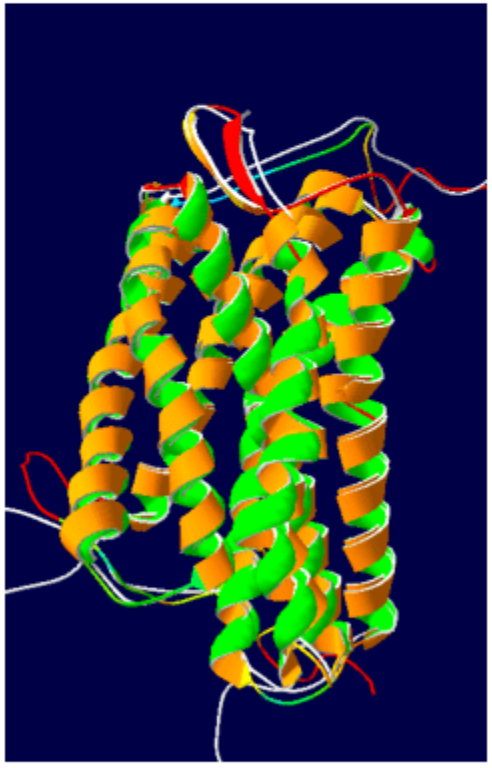


Comparing Structures -
Natural & CCR4 Variant, Superimposed

The two structures are nearly identical.

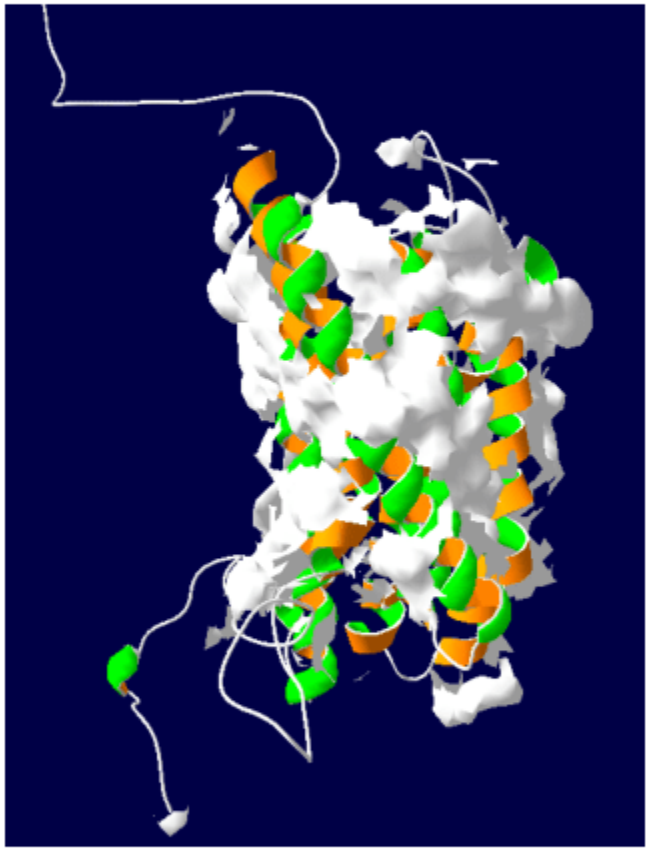


View #1

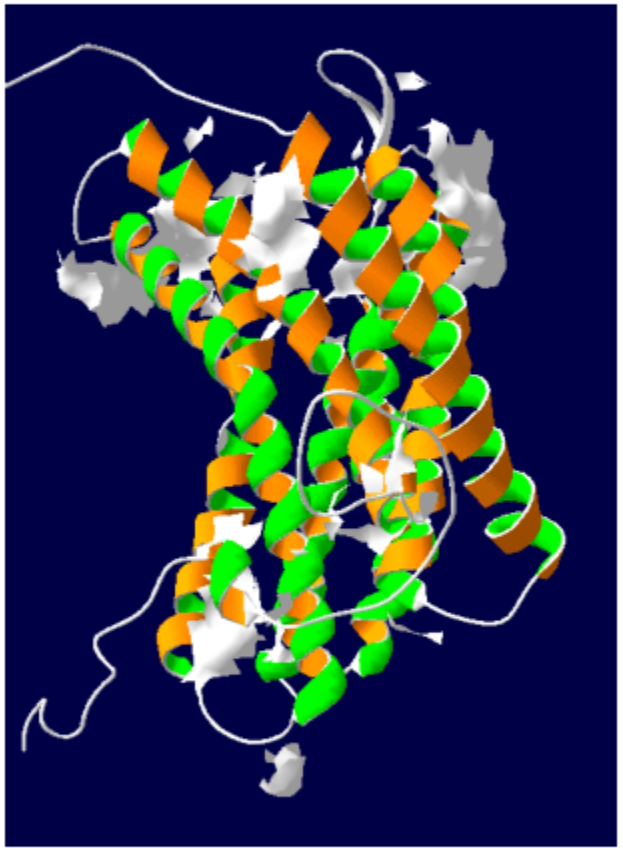


View #2

Comparing H20 Solubility



Natural CXCR4
Hydrophobic Regions

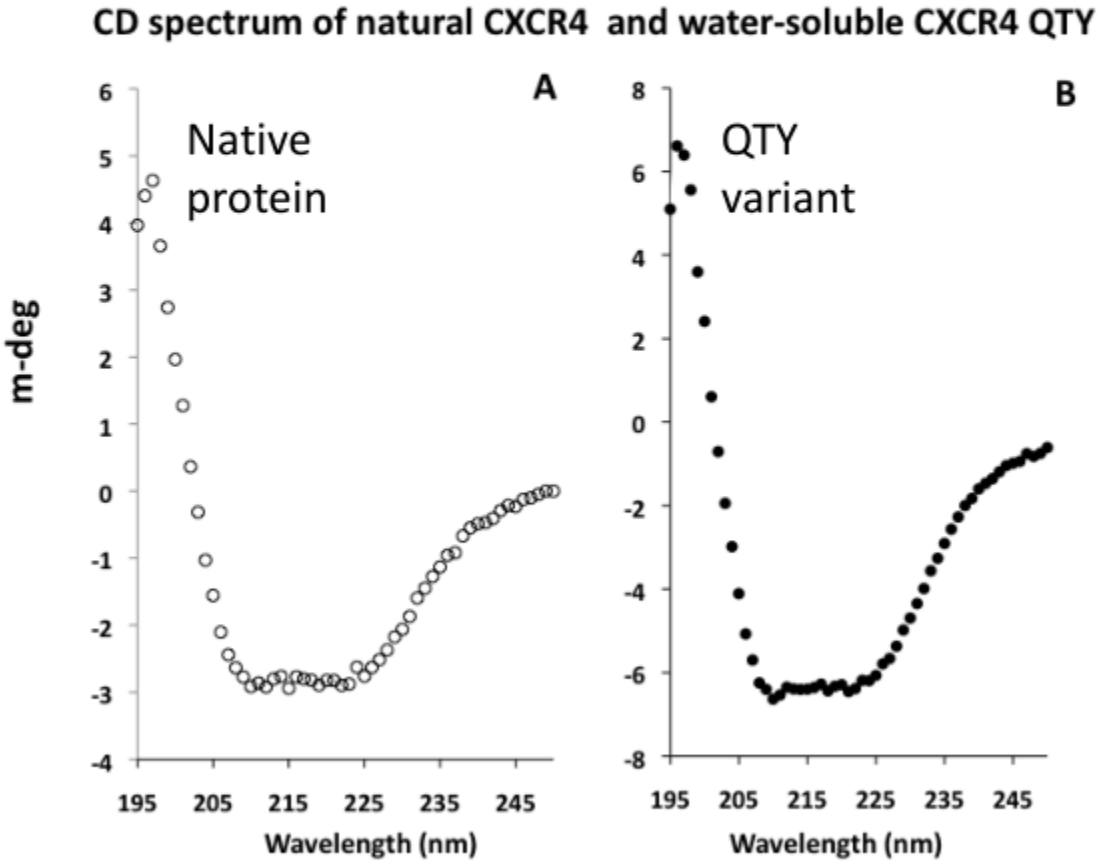


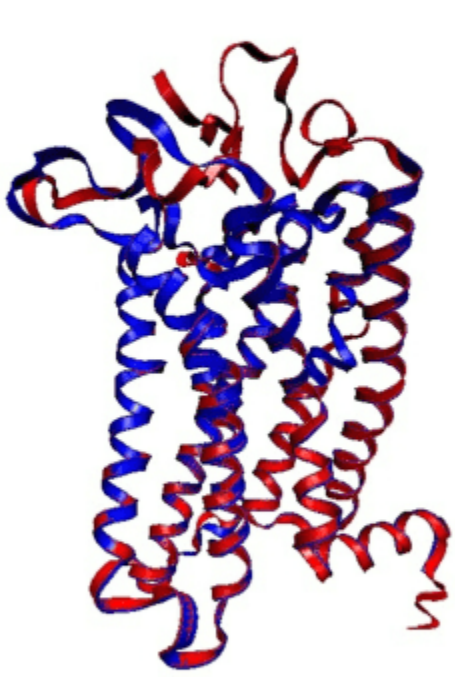
Designed Variant CXCR4^{QTY}
Hydrophobic Regions

Native CXCR4 and CXCR4 variant

The CD spectra

Molecular models



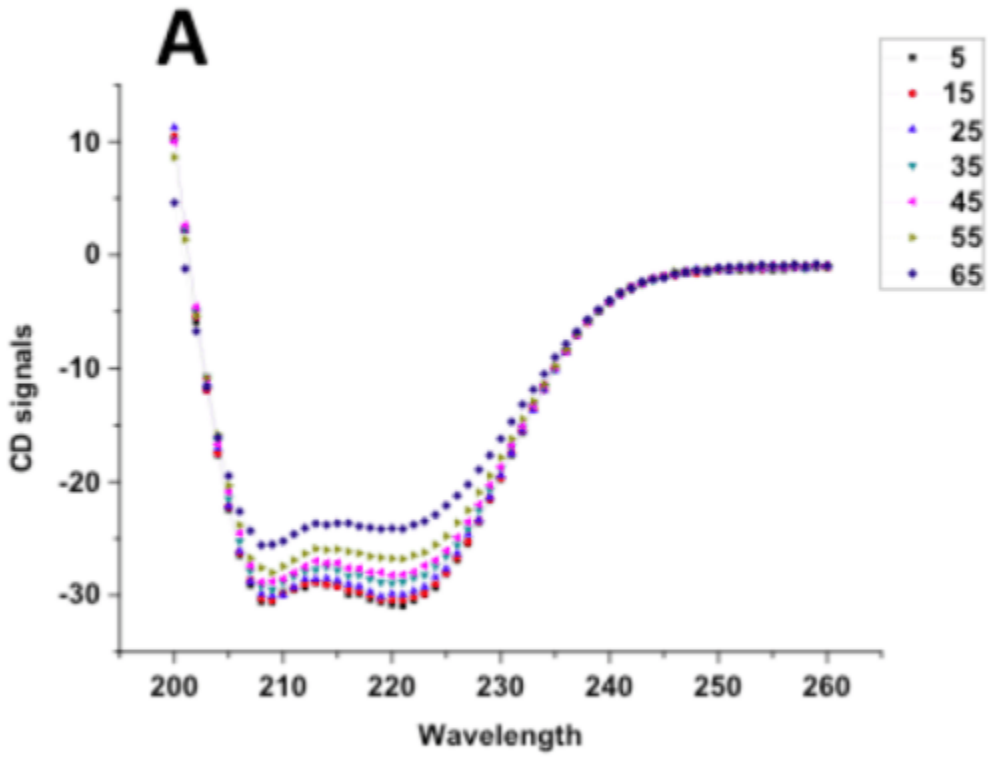


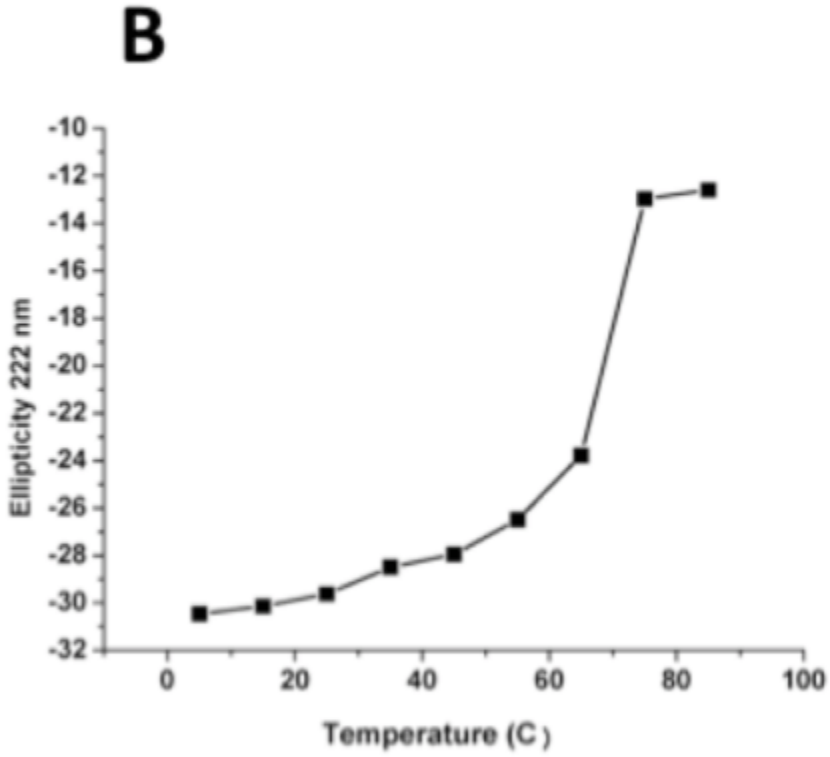
Red, Native CXCR4

Blue, CXCR4^{QTY} variant

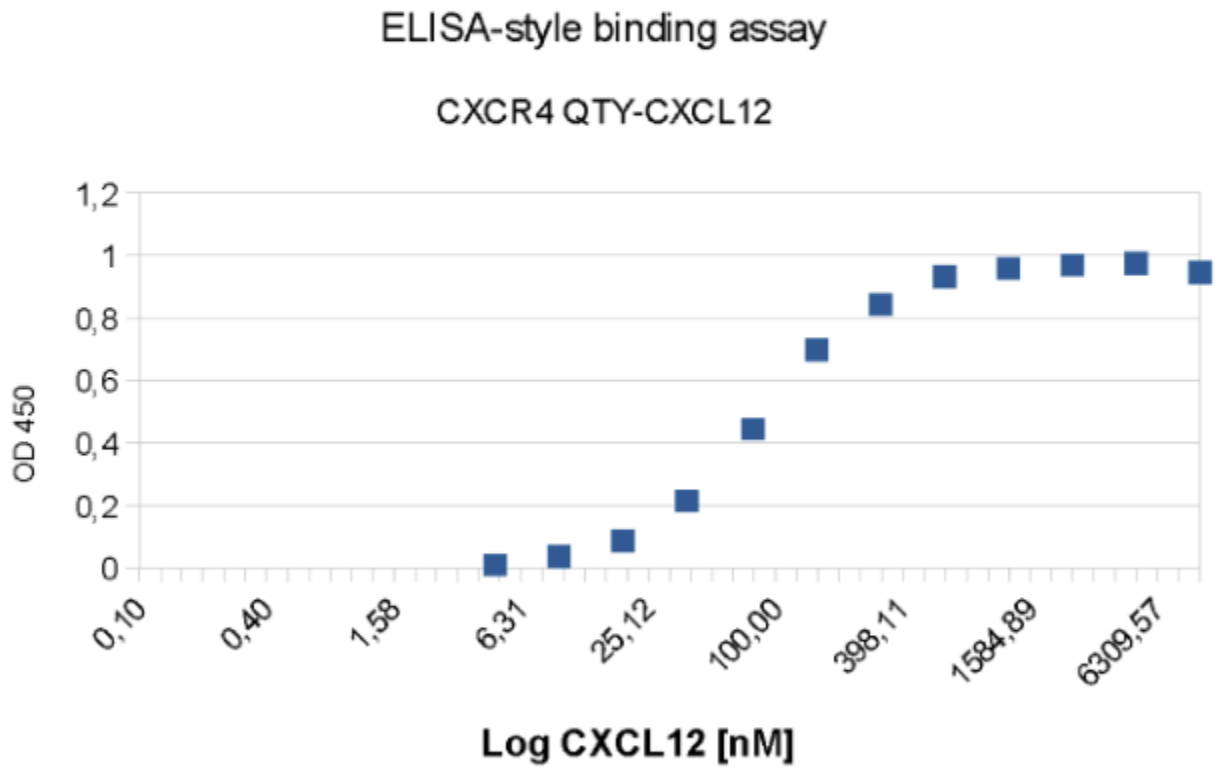
The structures are nearly The same.

Thermal Stability of Water-soluble CXCR4^{QTY}, Tm 67˚C



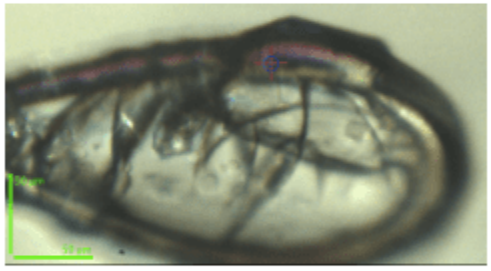


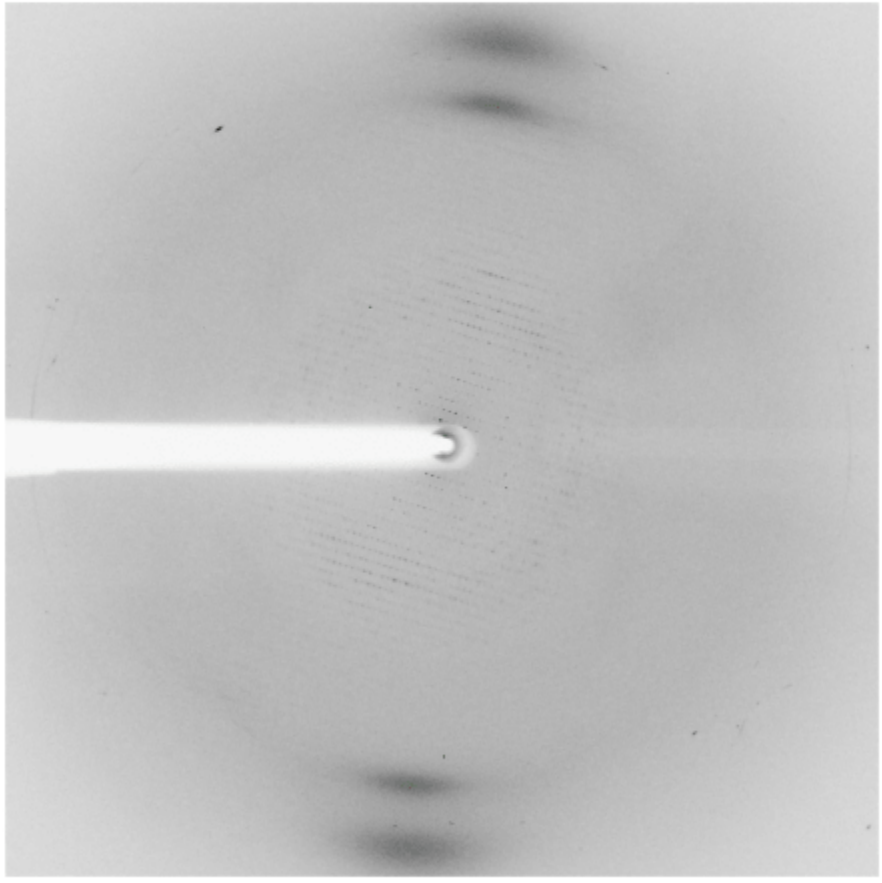
Ligand-binding of CXCR4^{QTY} with its natural ligand CXCL12



The natural SDF1a ligand-binding assay. The SDF1a binds to the native CXCR4 ~100nM.
The SDF1a binds to the designed code made CXCR4 variant ~80nM.

X-ray diffraction of crystal of water-soluble CXCR4^{QTY}





First Patent Issued

US008637452B2

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

(10) **Patent No.: US 8,637,452 B2**
(45) **Date of Patent: Jan. 28, 2014**

(54) **WATER SOLUBLE MEMBRANE PROTEINS AND METHODS FOR THE PREPARATION AND USE THEREOF**

(75) Inventors: **Shuguang Zhang**, Lexington, MA (US); **Alexander Rich**, Cambridge, MA (US); **Karolina Corin**, Irvine, CA (US); **Lotta T. Tegler**, Linköping (SE)

(73) Assignee: **Massachusetts Institute of Technology**, Cambridge, MA (US)

2011/0028700	A1	2/2011	Heal
2011/0046351	A1	2/2011	Weir et al.
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2012/0165507	A1	6/2012	Jazayeri-Dezfuly et al.

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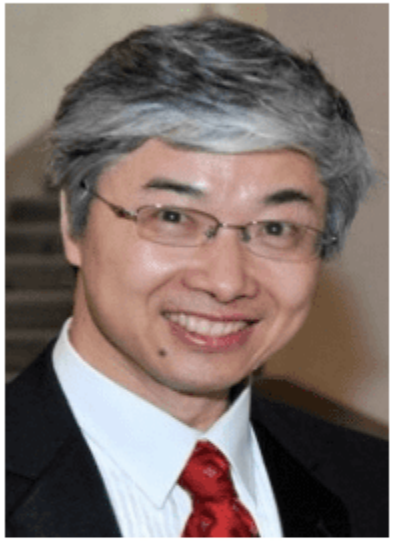
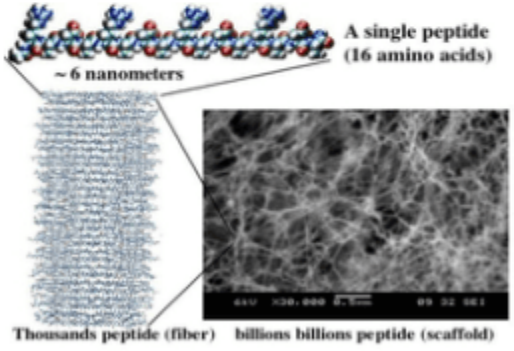
WO	2011/095625	A1	8/2011	
WO	2012/066330	A1	5/2012	
WO	2012/098413	A1	7/2012	
WO	2012/120315	A2	9/2012	

Zhang, S and Tao Fei, Design Code for Design code of detergent-free G protein-coupled receptors substituting hydrophobic amino acids using non-ionic amino acids and uses thereof. MIT case No. 16938X (To be filed in 2014)

Shuguang Zhang, Ph.D.



Inventor of self-assembling Peptide nanofiber scaffolds



Academic Biography

- Institute: Center for Bits and Atoms, MIT
- Alma mater: PhD, Biochemistry & Molecular Biology, Department of Biological Sciences, University of California, B.S., Sichuan University, China.
- Award: Winner of R&D100 award for peptide matrix, Wilhelm Exner Medal of Austria. Fellow of US National Academy of Inventors, Fellow of American Institute of Medical & Biological Engineering.
- Foreign Member of the Austrian Academy of Sciences in Vienna, Fellow of the American Institute of Medical & Biological Engineering, Honorary Professor of China University of Petroleum and Sichuan & Shanghai Jiaotong University.
- 16 issued patents and 20 pending patent applications.
- Published over 170 scientific papers.

Business Biography

- Co-founder of biotech startups 3-D Matrix., Ltd. (7777:JP), IPO in Japan in 2011 October on JASDAQ (current valuation
- ~$800 millions September 2014).
- Co-Founder and Board member of Molecular Frontiers Foundation, a global organization with objective to early identify breakthroughs in science and to stimulate young people's interests in science.

Robert S. Langer, Sc.D.

Father of controlled drug release & tissue engineering

Academic Biography

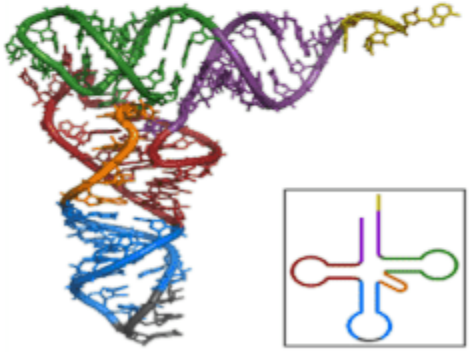
- Institutions: David H. Koch Institute Professor at the Massachusetts Institute of Technology
- Alma mater: Cornell University (Sc.D.), Massachusetts Institute of Technology (B.C.)
- Awards: Priestley Medal, US National Medal of Science, 10th Annual Heinz Award in the category of Technology, Economy and Employment, Charles Stark Draper Prize, Lemelson-MIT Prize, Albany Medical Center Prize in Medicine and Biomedical Research, Millennium Technology Prize.
- Member of US National Academy of Sciences, of Engineering and of Institute of Medicine.
- Considered a pioneer of many new technologies, including transdermal delivery systems, which allow the administration of drugs or extraction of analytes from the body through the skin without needles or other invasive methods, and the creation of engineered blood vessels and vascularized engineered muscle tissue.
- Maintained a research laboratory at MIT, which is the largest biomedical engineering lab in the world, maintaining about $10 million in annual grants and over 100 researchers.
- Held more than 1020 granted or pending patents.
- Authored more than 1,100 scientific papers.

Business Biography

- Participated in the founding of multiple technology companies.
- Co-Founders for over 25 biotechnology companies.
- Board members, scientific advisors and consultants for ~100 entities.
- Generated over $100 billion biotech business worldwide annually.

Alexander Rich, M.D.

Discover of structures of collagen, RNA double helix, tRNA, Z-DNA



Academic Biography

- **Institutions: The William Thompson Sedgwick Professor of Biophysics at MIT since 1958.**
- **Alma mater: A.B. Harvard University and an M.D. from Harvard Medical School.**
- **Awards: US National Medal of Science, MIT James Killian Award, Linus Pauling Medal, Lewis Rosenstiel Award, William Procter Prize, Lomonosov Medal, Passano Award, Bower Award and the Welch Award.**
- **Member of US National Academy of Sciences, Institute of Medicine and Philosophical Society. Foreign member of French Academy of Sciences, Russian Academy of Sciences and Pontifical Academy of Sciences.**
- **5 Honorary Ph.D. from ETH-Zurich, Weizmann Institute of Science, Freie University-Berlin, Federal University of Rio de Janerio and Sichuan University, China.**
- **Discovered nuclei acid hybridization, RNA double helix, DNA-RNA hybrid double helix, molecular structure of collagen, of tRNA, of DNA-anticancer drug complexes and polyribosomes.**
- **Determined the molecular structure of left-handed double helix Z-DNA. This was the first single crystal structure of any form of DNA, published on the cover of Nature in Dec 1979. After 26 years of attempts, Rich and colleagues finally determined molecular structure of the junction of B-DNA and Z-DNA. Their results were again published on the cover in Nature in Oct 2005.**
- **Editorial board of more than 20 journals including Science, PNAS, J.Mol. Biol., EMBO J., RNA and Genomics.**

Business Biography

- **Co-Founder and the Co-Chairman of the Board of Directors of Repligen Corporation (NASDAQ: RGEN), a biopharmaceutical company since 1981.**
- **Co-Founder and Board of Directors , Alkermes , Inc. (NASDAQ: ALKS) and has been its director since 1987.**
- **Co-Founder 3DMatrix, Inc., Tokyo, Japan, 2002; Co-Founder and Board of Directors for Profectus BioSciences, Inc. 2004; Co-Founder, Beaver Biosciences, Guangzhou, China, 2009.**
- **Scientific Advisor for 11 biotech companies.**

Next Steps/Raise

Our next step is to demonstrate our process on 14 GPCRs simultaneously, as a final proof of concept. This work will take 4 months. At that milestone, we will publish scientific papers, raise money to form our first spin out company.

Current raise:
$800K in convertible notes at a 30% discount to Series A