

Gary Charles Look, Ph.D.

Professional Experience:

Look BioPharma Consulting, Santa Clara, CA 2009 to present
A sole-proprietorship focused on drug discovery consulting and program management services.

Owner/Consultant

- Consulting services for industrial and academic clients.
- Recent clients have focused on cancer and neurodegenerative disease therapeutics.
- Activities included: program and technology evaluation, assistance in the writing of patent applications, creation and upkeep of competitive intelligence database, identification and recommendation of contract research laboratories, assistance in the preparation of grant applications, and the management of a medicinal chemistry program.
 - Developed a lead compound into multiple orally available pre-IND candidates with demonstrated efficacy in animal models for a client.
 - Co-inventor of investigational drug CT1812, a negative allosteric Sigma-2 receptor modulator for the treatment of patients with Alzheimer's disease.
 - Directed CRO-based medicinal chemistry program (8 China-based FTE).
 - Coordinated CRO-based lead compound scale-up to kg scale with compound quality control.
 - Coordinated CRO-based in vitro and in vivo ADME, PK, and toxicology studies.
 - Improved lead non-oral small molecule lead compound into an orally available development candidate with demonstrated efficacy in animal models and with a two-fold increase in microsomal stability, and target selectivity.
 - 3rd generation oral compounds have up to 3-fold increase in stability, 10-fold increase in target selectivity and single digit nanomolar potency.
 - Participant in clinical development team. Member of CMC oversight committee.
 - Experienced in working in collaborations with Academic partners
 - Proficient with Collaborative Drug Discovery CDD Vault database
 - Familiarity at working with Twiddlebit Plan for Windows (Gantt charts).

Acumen Pharmaceuticals, Inc., South San Francisco, CA 2006 to 2008
Acumen Pharmaceuticals is a pre-IPO biotechnology company specializing in the discovery of new technologies for the diagnosis and treatment of Alzheimer's disease. Research was focused on the inhibition of soluble amyloid oligomer assembly and the identification of the amyloid receptor. The assembly blocker program was suspended due to funding limitations. The program was eventually licensed to Mertz Pharma.

Staff Scientist - Project Leader for the assembly blocker program

- Managed the small molecule drug discovery program directed towards the inhibition of the assembly and binding of soluble amyloid beta oligomers as Alzheimer's disease modifying therapeutics. The work in this area resulted in the discovery of several lead series with efficacy in animal models and the advancement of compounds into pre-clinical development.
- Managed outsourced medicinal and computational chemistry, ADME, and PK programs.
- Developed and implemented project plans and coordinated with contract laboratories and internal teams.
- Over a four month period, directly supervised two biologists in the optimization of a screening assay and the rescreening of the 100K member company compound collection.
- Overhauled and improved the biochemical screening assay and data transformation algorithms for the assembly blocker program. This work led to the implementation of a more robust automated screening protocol for the biochemical assay and a more rigorous protocol for the handling of assay data.

Rigel Pharmaceuticals, Inc., South San Francisco, CA

2002 to 2005

Rigel Pharmaceuticals is a small biotechnology company specializing in anticancer, anti-inflammatory, and anti-infective drug discovery and development. In March 2005, the company discontinued drug discovery efforts in my project area.

Senior Scientist/Senior Scientist II

- Provided contributions to drug discovery research program targeting ubiquitin pathway enzymes in the oncolytic and inflammatory therapeutic areas. The work in these areas culminated in the discovery of lead series in several classes of ubiquitin processing enzymes and the filing of several provisional patent applications.
- Managed collaboration with the NCI Developmental Therapeutics Program to test lead compounds. Responsible for the establishment of a screening agreement with the NCI and for the selection, resynthesis, and shipment of compounds. This effort led to the discovery of a low nanomolar compound against several NCI cell lines.

Signature BioScience, Inc., Richmond, CA (Defunct)

February to April 2002

Signature BioScience was a pre-IPO pharmaceutical firm specializing in anticancer drug discovery and development. The company was unable to secure necessary funding and discontinued business in April 2003.

Staff Scientist

- Contributed towards the continued optimization of the lead oncolytic compound series, which was originally discovered at Protein Design Labs. The work in this area resulted in the discovery of two classes of compounds, which were advanced to preclinical development.

Protein Design Labs, Inc., Fremont, CA

1998 to 2002

Protein Design Labs, Inc. is a biotechnology company specializing in therapeutic humanized antibodies that initiated a therapeutic small molecule discovery effort in 1998. I was the second chemist hired at the company. PDL sold their small molecule effort to Signature BioScience in January 2002.

Senior Scientist

- Assisted in the setup of a new chemistry program within an established company.
- Led the development of parallel synthesis technologies to support various therapeutic efforts within PDL – including the acquisition and implementation of robotic liquid handlers and the IRORI automated system and the design of library preparation tools.
- Worked with computational chemistry group and proprietary software to design pharmacophore models.
- Led a team of chemists optimizing the SAR of oncolytic and anti-infective leads. This work culminated in the discovery of lead series in both therapeutic areas. These series were further examined by Signature BioScience and have resulted in the filing of several provisional patent applications.
- Led a team of five chemists in the design and production of screening libraries.
- Provided chemistry leadership during director's extended absence.

MetaXen, LLC, Hayward, CA (Defunct)

1997 to 1998

MetaXen was a pre-IPO biotechnology company specializing in thrombosis therapeutics drug discovery and development. I was the first chemist hired at the company. I left in 1998 to aid in the initiation of the small molecule drug discovery effort at PDL. In 1999, the company was sold to Exelixis.

Senior Scientist

- Assisted in the setup of a new chemistry program within a startup company.
- Worked with the Vice President of Research and an external contractor to screen and recruit senior chemistry staff.
- Contributed to the development and optimization of compounds discovered by corporate partners.
- Worked with the pharmacology and computational chemistry groups to generate, test, and validate pharmacophore models. This work resulted in the discovery of a lead series in the thrombolytic area.
- Coordinated contract work with an outside collaborator on a medicinal chemistry project.

RedCell, Inc., South San Francisco, CA (Defunct)

1996 to 1997

RedCell was a pre-IPO biotechnology company specializing in novel drug delivery systems via the attachment of therapeutics to blood proteins. The company was unable to secure necessary funding and ceased operations in the USA in 1997. The company was purchased and relocated to Canada.

Senior Scientist

- Contributed to the development of new chemical technologies for the specific attachment of therapeutic agents to blood proteins.

Affymax Research Institute, Palo Alto, CA

1993 to 1996

Affymax Research Institute was a small biotechnology company specializing in novel drug discovery technologies and was engaged in drug discovery in multiple therapeutic areas. In 1995, Glaxo purchased the company.

Staff Scientist

- Provided contributions to the development of novel small molecule templates in support of an externally funded metalloprotease project. This work resulted in the filing of several patent applications.
- Provided contributions to the development of new technologies and chemical methods for the synthesis of small molecules on solid support. This work led to the publication of several papers in the field of combinatorial chemistry.
- Designed and implemented the synthesis of early proof-of-concept small molecule libraries for the solid-supported synthesis and screening of compounds.

Other Relevant Professional Experience:**Foley & Lardner, LLP**, Palo Alto, CA

May to August 2008

Foley & Lardner is a privately held law firm. This was a temporary position within the Chemical and Pharmaceutical Practice Group of the Intellectual Property Department.

Senior Technical Specialist

- Assisted in the preparation of responses to Office Actions.
- Assisted in the drafting of patent applications.
- Prepared Information Disclosure Statements/SB08's.
- Performed background IP research.
- Performed preliminary analysis of patent portfolios.

Education:

Postdoctoral Research: 1990-1992 - American Cancer Society Postdoctoral Fellow - The Scripps Research Institute, La Jolla with Professor Chi-Huey Wong

Ph.D., Organic Chemistry: 1990 - The University of California, Irvine with Professor Larry E. Overman

B.S., Chemistry: 1985 - The University of California, Berkeley

Undergraduate Research with Professors William G. Dauben and Andrew Streitwieser, Jr

Professional Training Courses:

Zenger-Miller Frontline Leadership management six-week course	1999
ACS Short Course: "Antibiotics and Antibacterial Agents"	2000
ACS Short Course: "Pharmacology for Chemists"	2001
Rigel In-House Short Course on Drug Metabolism	2004
ACS Short Course: "Fundamentals of Pharmacokinetics"	2007
ACS Short Course: "Integration of DMPK, Toxicology and Biopharmaceutics in the Identification, Optimization and Selection of Clinical Candidates"	2007

Affiliations and Activities:

Society for Neuroscience

Royal Society of Chemistry (U.K.) member and Chartered Chemist

American Chemical Society: Medicinal and Organic division

International Society of Heterocyclic Chemistry

American Association for the Advancement of Science

Publication List:

“Discovery of Investigational Drug CT1812, an Antagonist of the Sigma-2 Receptor Complex for Alzheimer's Disease” Rishton GM, Look GC, Ni ZJ, Zhang J, Wang Y, Huang Y, Wu X, Izzo NJ, LaBarbera KM, Limegrover CS, Rehak C, Yurko R, Catalano SM. *ACS Med Chem Lett.* 2021 Sep 9;12(9):1389-1395. PubMed Central PMCID: PMC8436239.

“Sigma-2 receptor antagonists rescue neuronal dysfunction induced by Parkinson's patient brain-derived α -synuclein.” Limegrover CS, Yurko R, Izzo NJ, LaBarbera KM, Rehak C, Look G, Rishton G, Safferstein H, Catalano SM. *J Neurosci Res.* 2021 Apr;99(4):1161-1176. PubMed Central PMCID: PMC7986605.

“Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification.” 3. Izzo NJ, Yuede CM, LaBarbera KM, Limegrover CS, Rehak C, Yurko R, Waybright L, Look G, Rishton G, Safferstein H, Hamby ME, Williams C, Sadlek K, Edwards HM, Davis CS, Grundman M, Schneider LS, DeKosky ST, Chelsky D, Pike I, Henstridge C, Blennow K, Zetterberg H, LeVine H 3rd, Spires-Jones TL, Cirrito JR, Catalano SM. *Alzheimer's Dement.* **2021**;1-18.

“Sigma-2 receptor antagonists rescue neuronal dysfunction induced by Parkinson's patient brain-derived α -synuclein.” Limegrover CS, Yurko R, Izzo NJ, LaBarbera KM, Rehak C, Look G, Rishton G, Safferstein H, Catalano SM. *J Neurosci Res.* **2021** Jan 22;PubMed PMID: 33480104.

“Alzheimer's Therapeutics Targeting Amyloid Beta 1-42 Oligomers I: Abeta 42 Oligomer Binding to Specific Neuronal Receptors Is Displaced by Drug Candidates That Improve Cognitive Deficits” Izzo, N.J.; Staniszewski, A.; To, L.; Fa, M.; Teich, A. F.; Saeed, F.; Wostein, H.; Walko III, T.; Vaswani, A.; Wardius, M.; Syed, Z.; Ravenscroft, J.; Mozzoni, K.; Silky, C.; Rehak, C.; Yurko, R.; Finn, P.; Look, G.; Rishton, G.; Safferstein, H.; Miller, M.; Shamloo, M.; Arancio, O.; LeVine III, H.; Catalano, S. M. *PLoS One* **2014**, *10*, e0111898.

“Alzheimer's Therapeutics Targeting Amyloid Beta 1-42 Oligomers II: Sigma-2/Pgrmc1 Receptors Mediate Abeta 42 Oligomer Binding and Synaptotoxicity” Izzo, N. J.; Xu, J.; Zeng, C.; Kirk, M. J.; K. Mozzoni, K.; Silky, C.; Rehak, C.; Yurko, R.; Look, G.; Rishton, G.; Safferstein, H.; Cruchaga, C.; Head, E.; LeVine III, H.; Spires-Jones, T. L.; Catalano, S. M. , *PLoS One* **2014**, *10*, e0111899.

“The Discovery of Biaryl Acids and Amides Exhibiting Antibacterial Activity Against Gram Positive Bacteria” Look, G. C.; et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1423.

“Novel Antimicrobials from Encoded Combinatorial Libraries Using 2D Agar Format” Silen, J. L.; et al. *Antimicrobial Agents and Chemotherapy* **1998**, *42*, 1447.

“A Novel Reductive Amination Procedure Applicable to Both Solid Phase and Solution Phase Syntheses” Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Patel, D. V.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720.

“The Identification of Cyclooxygenase-1 Inhibitors from 4-Thiazolidinone Combinatorial Libraries” Look, G. C.; Schullek, J. R.; Holmes, C. P.; Chinn, J. P.; Gordon, E. M.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 707.

“Strategies for Combinatorial Synthesis: Solution and Polymer-Supported Synthesis of 4-Thiazolidinones and 4-Metathiazolidinones Derived from Amino Acids” Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *50*, 7328.

“Trimethylorthoformate: A Mild and Effective Dehydrating Reagent for Solution and Solid Phase Imine Formation” Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

“Methods for Combinatorial Synthesis: The Use of Fast ^{13}C NMR Analysis for Solid Phase Reaction Monitoring” Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.

“Simple Method for Controlling Stereoselection in Mannich Cyclization Reactions of Aldehydes” Heerding, D. A.; Hong, C. Y.; Kado, N.; Look, G. C.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 6948.

“A Combined Chemical and Enzymatic Strategy for the Construction of Carbohydrate-Containing Antigen Core Units” Look, G. C.; Ichikawa, Y.; Shen, G. J.; Cheng, P. W.; Wong, C. H. *J. Org. Chem.* **1993**, *58*, 4326.

“Chloroperoxidase-Catalyzed Asymmetric Synthesis: Enantioselective Reactions of Chiral Hydroperoxides with Sulfides and Bromohydroxylation of Glycals” Fu, H.; Kondo, H.; Ichikawa, Y.; Look, G. C.; Wong, C. H. *J. Org. Chem.* **1992**, *57*, 7265.

“A Facile Enzymatic Synthesis of Gal β 1,3Glucal: A Key Intermediate for the Synthesis of Le^a and Sialyl Le^a” Look, G. C.; Wong, C. H. *Tetrahedron Lett.* **1992**, *33*, 4253.

“Mechanistic Study of a Synthetically Useful Monooxygenase Model Using the Hypersensitive Probe Trans-2-Phenyl-1-Vinylcyclopropane” Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C. H. *J. Org. Chem.* **1991**, *56*, 6497.

“Probing Acceptor Specificity of β 1,4-Galactosyltransferase for the Enzymatic Synthesis of Novel Oligosaccharides” Wong, C. H.; Ichikawa, Y.; Krach, T.; Gautheron-Le Narvor, C.; Dumas, D. P.; Look, G. C. *J. Am. Chem. Soc.* **1991**, *113*, 8137.

“A New Approach to the Synthesis of Novel Oligosaccharides Based on Glycosyltransferases: β 1,4-Galactosyltransferase” Wong, C. H.; Krach, T.; Gautheron-Le Narvor, C.; Ichikawa, Y.; Look, G. C.; Gaeta, F.; Thompson, D. D.; Nicolaou, K. C. *Tetrahedron Lett.* **1991**, *32*, 4867.

“Preparation of Eight-Membered Cyclic Ethers by Lewis Acid-Promoted Acetal-Alkene Cyclizations” Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386.

“Formation of Δ^4 -Oxocenes from Lewis Acid Promoted Cyclizations of 5-Hexenyl Acetals. Evidence for a Concerted Ene Cyclization Mechanism” Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.

“Pyridinium Carbons: Perpyridinium Derivatives of Cyclopropene and Allyl Anion” Waterman, K. C.; Speer, D. V.; Streitwieser, A., Jr.; Look, G. C.; Nguyen, K. O.; Stack, J. G. *J. Org. Chem.* **1988**, *53*, 583.

“Organic Reactions at High Pressure. The Effect of Pressure Change Upon Reaction Rates of Bimolecular Processes” Dauben, W. G.; Gerdes, J. M.; Look, G. C. *Synthesis* **1986**, 532.

“Organic Reactions at High Pressure. Conversion of Cyclic Alkanones and Enones to 1,3-Dioxolanes” Dauben, W. G.; Gerdes, J. M.; Look, G. C. *J. Org. Chem.* **1986**, *51*, 4964.

Book Chapters and Reviews:

“Discovery of ADDL-Targeting Small Molecule Drugs for Alzheimer’s Disease” Look, G.C.; Jerecic, J.; Cherbavaz, D.B.; Pray, T.R.; Breach, J.R.; Crosier, W.J. et al. *Curr. Alzheimer’s Res.* **2007**, *4*, 562-567.

“Analytical Issues in Combinatorial Drug Discovery” Fitch, W. L.; Look, G. C.; Detre, G. in *Combinatorial Chemistry and Molecular Diversity* Gordon, E. M.; Kerwin, J. F., Jr., eds. Wiley, 1998, pp. 349-368.

“Combinatorial Organic Synthesis: Applications to Drug Discovery” Gordon, E. M.; Gallop, M. A.; Campbell, D.; Holmes, C.; Bermak, J.; Look, G.; Murphy, M.; Needels, M.; Jacobs, J.; Sugarman, J.; Chinn, J.; Ruhland-Fritsch, B.; Jones, D. *Proc. XIIIth Int. Symp. Med. Chem.* **1995**, *30*, 337s.

“Recent Developments in Enzymatic Synthesis of Oligosaccharides and Glycopeptides” Ichikawa, Y.; Look, G. C.; Shen, G. J.; Sears, P.; Wang, P.; Wong, C. H. in *Carbohydrates and Carbohydrate Polymers, Analysis, Biotechnology, Modification, Antiviral, Biomedical, and Other Applications* Chapter 1, Yalpani, M., ed. ATL Press 1993.

“Enzyme-Catalyzed Organic Synthesis: Practical Routes to Aza Sugars and their Analogs for Use as Glycoprocessing Inhibitors” Look, G. C.; Fotsch, C. H.; Wong, C. H. *Acc. Chem. Res.* **1993**, *26*, 182.

“Chemical-Enzymatic Synthesis of Carbohydrates” Wong, C. H.; Ichikawa, Y.; Kajimoto, T.; Liu, K. K. C.; Dumas, D. P.; Lin, Y. C.; Look, G. C. in *Microbial Reagents in Organic Synthesis*, NATO ASI Series, Ser. C, **1992**, *381*, 35.

“Synthesis of Oligosaccharides Using Glycosyltransferases” Ichikawa, Y.; Look, G. C.; Wong, C. H.; Kajimoto, T. *Synth. Org. Chem., Jpn.* **1992**, *50*, 441.

“Enzymatic Oligosaccharide Synthesis” Ichikawa, Y.; Look, G. C.; Wong, C. H. in *Glycotechnology* Oga-
wa, T.; Nagai, T., eds. **1992**, p. 495.

“Enzyme-Mediated Oligosaccharide Synthesis” Ichikawa, Y.; Look, G. C.; Wong, C. H. *Anal. Biochem.* **1992**, *202*, 215.

Patents:

“Compositions for treating neurodegenerative diseases.” Rishton GM, Look GC, Catalano SM, US Patent No, 11214540. (2022).

“Isoindoline compositions and methods for treating neurodegenerative disease.” Rishton, Gilbert; Catalano, Susan M.; Look, Gary C. US Patent No. 16611728 (continuation) (2020).

“Isoindoline compositions and methods for treating neurodegenerative disease.” Rishton, Gilbert; Catalano, Susan M.; Look, Gary C. US Patent No. 10207991 (continuation) (2019).

“Isoindoline compositions and methods for treating neurodegenerative disease.” Rishton, Gilbert; Catalano, Susan M.; Look, Gary C. US Patent No. 9796672 (2017).

“Preparation of terphenyl-3-carboxamides as topoisomerase inhibitors” Murphy, Martin A.; Schullek, John Robert; Ward, John S.; Look, Gary C.; Siesel, Brian. U.S. Patent No. 7683097 (2010).

“Rhodanine compositions for use as antiviral agents” Singh, Rajinder; Ramesh, Usha; Issakani, Sarkiz D.; Look, Gary Charles U.S. Patent No. 7566732 (2009).

“Collagenase-1 and stromelysin-1 inhibitors, pharmaceutical compositions comprising same and methods of their use” Campbell, David; Look, Gary C.; Szardenings, Anna Katrin; Patel, Dinesh V. U.S. Patent No. 6271232 (2001).

“Inhibitors of metalloproteases pharmaceutical compositions comprising same and methods of their use” Campbell, David; Look, Gary C.; Szardenings, Anna Katrin; Patel, Dinesh V. U.S. Patent No. 5990112 (1999).

“Preparation of mercaptomethyldiketopiperazines as collagenase-1 and stromelysin-1 inhibitors” Campbell, David; Look, Gary C.; Szardenings, Anna Katrin; Patel, Dinesh V. U.S. Patent No. 5932579 (1999).

“Enzymatic process for producing a galactosyl- β -1,3-glycal disaccharide using β -galactosidase” Wong, Chi Huey; Look, Gary C. Cont.-in-part of US Ser. No. 910612. U.S. Patent No. 5403726 (1995).

Published Patent Applications:

“Methods for treating neurodegenerative diseases” Rishton, Gilbert; Catalano, Susan M.; Look, Gary C. PCT Publication No. WO2018/213281.

“GGA Derivatives” Look, Gary C. PCT Publication No. WO 2015006614.

“Methods of inhibiting the formation of amyloid-beta diffusible ligands using acylhydrazide compounds” Look, Gary Charles; Schultz, Lauri; Polozov, Alexandre Mikhaylovich; Bhagat, Nikhil; Wang, Jian; Zembower, David E.; Goure, William F.; Pray, Todd; Krafft, Grant A. U.S. Pat. Appl. Publ. (2011), US 20110098309.

“N-aryl piperidine” Murphy, Martin A.; Schullek, John Robert; Ward, John S.; Look, Gary C.; Jain, Rama; Lee, Laurance US Patent Application No. US20060035932.

“Topoisomerase inhibitors” Murphy, Martin A.; Schullek, John Robert; Wards, John S.; Look, Gary C.; Siesel, Brian PCT Publication No. WO 2006022955.

“N-aryl piperidine compounds for inhibiting hiv infection” Murphy, Martin A.; Schullek, John Robert; Ward, John S.; Look, Gary C.; Jain, Rama; Lee, Laurance PCT Publication No. WO 2005120503.

“Ubiquitin ligase inhibitors” Ramesh, Usha; Look, Gary; Huang, Jianing; Singh, Rajinder; Mattis, Richard Brent US Patent Application No. US20050282818.

“Benzothiazole and thiazole 5',5-bipyridine compositions and their use as ubiquitin ligase inhibitors” Parlati, Francesco; Ramesh, Usha V.; Singh, Rajinder; Payan, Donald G.; Lowe, Raymond; Look, Gary Charles PCT Publication No. WO 2005037845.

“Preparation of biaryl ether sulfonamides and related derivatives as ubiquitin ligase inhibitors” Ramesh, Usha V.; Look, Gary Charles; Singh, Rajinder; Issakani, Sarkiz D. U.S. Patent Application No. US 2005009871.

“Preparation of 3-(mercaptomethyl)hexahydro-2,5-pyrazinedione derivatives as metalloprotease inhibitors” Campbell, David Alan; Look, Gary Charles; Szardenings, Anna Katrin; Patel, Dinesh Vinubhai PCT Publication No. WO 9748685.

“Solid phase synthesis of diketopiperazines (cyclodipeptides)” Campbell, David; Gallop, Mark A.; Gordon, Eric M.; Look, Gary C.; Patel, Dinesh V.; Szardenings, Anna Katrin PCT Publication No. WO 9600391.