The origins of chemical biology

Kim L Morrison & Gregory A Weiss

Chemical biology has historical roots that date back to the birth of chemistry and biology as distinct sciences.

The origins of chemical biology can be traced to the enormous technological and scientific advances of the nineteenth century, resulting in the field's ascent in the twentieth century. Examining the nineteenth-century origins of chemical biology serves at least two purposes. First, the history of science provides a framework for teaching. Descriptions of classic experiments and breakthroughs can equip teachers and students with examples illustrating key concepts. Second, the historical roots of chemical biology inform us that the field has always identified exciting new research questions and challenges. Such a record promises a bright future for the field.

Nature Chemical Biology defines chemical biology as both the use of chemistry to advance a molecular understanding of biology and the harnessing of biology to advance chemistry[1]. Despite the veneer of newness associated with the term, chemical biology has early, albeit modest, beginnings, extending back at least two centuries to the masterworks considered the foundations of chemistry and biology. This brief article presents a few intriguing histories that define the beginnings of chemical biology. Given its limited scope, however, many examples of the hard work, heartbreak, innovation and patience integral to the field have had to be omitted.

The history of nitrous oxide, discovered in 1772 by Joseph Priestley, provides a classic example of the yin and the yang of chemical biology. Inspired by Benjamin Franklin's work on electricity, the radical theologian Joseph Priestley (1733–1804) began to perform his own experiments on gases, referred to as 'airs' in the parlance of the time[2]. Priestley, perhaps most identified with the discovery of oxygen, also isolated at least ten other gases, including nitrous oxide. Using biology to advance chemistry, Priestley incubated mice with these gases. The approach provided a primitive characterization method (upon exposure to a compound, does a mouse live or die?) that has since fallen into disfavor with synthetic chemists. The experiments also inspired early animal-rights sentiments, including "The Mouse's Petition," a poem by Priestley's friend Anna Laetitia Aikin Barbauld (**Box 1**)[3]. Widespread condemnation of Priestley followed publication of the poem, fueling discontent with his radical political leanings, which included sympathy for the American colonies. Thus, an angry mob torched the home of perhaps the first chemical biologist.

Turning the tables on Priestley's approach to chemical biology by using chemistry to advance biology, Sir Humphrey Davy's experiments with newly isolated, unfamiliar gases omitted the mouse entirely. In what must be considered an act of either lunacy or egotism, Davy (1778–1829) carried out his experiments on himself. Not surprisingly, his experiments with carbon monoxide almost proved fatal. In one experiment, Davy inhaled four quarts of nitrous oxide isolated in a silk bag. The pleasant intoxicating effect of the gas inspired Davy to name it laughing gas. A popular drug in the late eighteenth century (and to a lesser extent today), nitrous oxide is believed to have influenced many of the celebrated works of one pleasure seeker, the author Samuel Taylor Coleridge[4]. Although Davy had noted the possible advantages of using nitrous oxide in surgical procedures, medical uses for the gas remained unexplored until experiments by the American dentist Horace Wells in 1844 (ref. 5). Application of the chemistry of nitrogen oxides to advance biology and medicine continues to the present day, reaching a high point with the 1998 Nobel Prize won by Robert Furchgott, Louis Ignarro and Ferid Murad for demonstrating the key roles played by nitric oxide in cell signaling.

©V&A Images/Victoria and Albert Museum (www.vam.ac.uk)

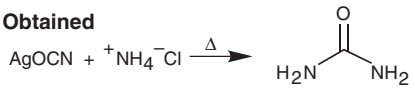
Figure 1 A cyanotype from *British and Foreign Flowering Plants and Ferns* by Anna Atkins (circa 1854). With characteristic artistry, Atkins captured two stages of feathery dandelion blossoms.

Establishing the importance of synthetic chemistry to chemical biology, Friedrich Wöhler's fortuitous accident in 1828 led the way to the formulation of a chemical basis for life. During an attempt to synthesize ammonium cyanate, Wöhler (1800–1882) heated a solution of silver cyanate and ammonium chloride. Separately, he also heated lead cyanate and aqueous ammonia. In both cases, he obtained not the expected product, but urea (**Scheme 1**)[6,7]. Wöhler's synthesis showed that inorganic starting materials could be used to synthesize substances previously associated

Gregory A. Weiss is in the Departments of Chemistry, Molecular Biology and Biochemistry, and Kim L. Morrison is in the Department of History at the University of California, Irvine, California 92697-2025, USA.
e-mail: gweiss@uci.edu

Expected

Obtained



Scheme 1 Wöhler's synthesis of urea. Yielding a chemical previously isolated only from man or dog, the synthesis of urea represented a landmark achievement in organic synthesis and chemical biology.

only with living organisms. In other words, chemical synthesis requires no 'living' or 'vital force' to make biologically active compounds. Remarkably, some belief in vitalism still persists within current popular culture. For example, the public continues to pay a premium for vitamins and other supplements isolated from natural sources[8]. Synthesis, of course, continues to play a key role in chemical biology, including the present frontiers of diversity-oriented synthesis and chemical genomics.

Another prevalent theme in contemporary chemical biology, cellular imaging, was revolutionized by chemical approaches first developed during the nineteenth century. One early innovator, Anna Atkins (1799–1871), learned science firsthand from her father, a prominent botanist, and his circle of friends, including Sir Humphry Davy, Sir John Herschel and William Henry Fox Talbot (the 'father of photography'). Herschel invented the cyanotype process for an intensely blue, monochromatic color photography[9]. The cyanotype process relies on light-sensitive paper doped with iron salts to produce negative images where the imaged sample blocks exposure to light. In her own time, Atkins established a solid reputation as a collector, botanist and scientific illustrator. Elected a member of the Botanical Society of London in 1839, a remarkable accomplishment for a woman in the mid-nineteenth century, Atkins applied Herschel's cyanotype process to document delicate botanical specimens (**Fig. 1**). Atkins published her images in the first photographically illustrated book (either scientific or nonscientific), *British Algae: Cyanotype Impressions* (1843)[10]. Atkins's photograms render a transparency to the stained objects, making the intricate details of her specimens remarkably clear. Art galleries, such as the Getty Museum in Los Angeles, still display her work[11].

Synthetic chemistry in the nineteenth century, especially the synthesis of aniline dyes, is inextricably linked to early cell biology. As improvements to microscopy and chemical dyes uncovered fine structures within the cell, Rudolf Virchow (1821–1902) published *Die Cellularpathologie* in 1858. This text established two key principles. First, all cells descend from other living cells, and, second, cellular changes can result in disease. Virchow's theory of cellular pathology transformed scientific understanding of biology and revolutionized the field of medicine. Virchow also bravely served in the German Reichstag in opposition to the Chancellor of "blood and iron," Otto von Bismarck[12]. Equally undaunted by hostility from his scientific peers, Virchow vehemently opposed germ theory, arguing instead that the causes of disease lay within the cells themselves. Discouraged and exasperated, Virchow eventually abandoned both politics and science for the seemingly more attainable goal of finding Homer's Troy. Nonetheless, Virchow's studies, particularly on leukemia, resulted in an explosion of interest in cell physiology and structure[13].

In 1856, as the Austrian monk Gregor Mendel began his studies of the genetic basis for heredity, an 18-year-old British chemist, William Perkin (1838–1907), worked diligently through the night in his laboratory seeking a treatment for malaria. While attempting to synthesize the alkaloid quinine, Perkin serendipitously discovered the first aniline dye, which he called mauveine for its brilliant violet color (**Fig. 2a**)[14]. Whereas the dazzle of mass-produced pigments transformed the fashion houses of Europe, the 1856 discovery of mauve had far-reaching implications for biological research, sparking the development of modern medicine[15]. For example, Paul Ehrlich realized the pharmaceutical potential of coal tar derivatives and suggested such treatments could provide 'magic bullets' for precise targeting of disease.

The cigar-smoking Ehrlich (1854–1915) devoted his early life's work to applying a chemical approach to the visualization of living cells. Ehrlich experimented with the newly discovered aniline dyes derived from coal tar and found that some dyes could differentially stain specific cells and tissues. He correctly surmised that this difference resulted from a chemical reaction of the dyes with specific substances within the cells[16]. For example, the predominant basicity of dyes capable of staining cell nuclei led Ehrlich to term the nucleus "basophilic." Applying the aniline methylene blue dyes for diagnostics, Ehrlich identified a tiny rod-shaped bacterium as the culprit responsible for tuberculosis. Ehrlich's insight into the intracellular reduction of various synthetic dyes led to amazing leaps in medicine, pioneering the earliest form of chemotherapy and drug therapy. For example, Ehrlich proposed the development of magic bullets or toxins capable of targeting specific pathogens. In the first example of a magic bullet, Ehrlich discovered a chemical, Salvarsan or Ehrlich's 606th (named in tribute to the 605 preceding failed compounds; **Fig. 2b**), to treat syphilis. Salvarsan became a blockbuster in its time and replaced the earlier treatment of mercury, which caused blackened teeth and baldness[17]. The success of Salvarsan paved the way for new drugs, ultimately fulfilling Perkin's initial experimental goal of finding a treatment for malaria.

Image copyright of Wellcome Library, London

Sir Humphry Davy (right, with bellows) presents his newly isolated airs to the Royal Institution, London. Caricature by James Gillray (1802). Image copyright and used with permission of the Wellcome Library, London.

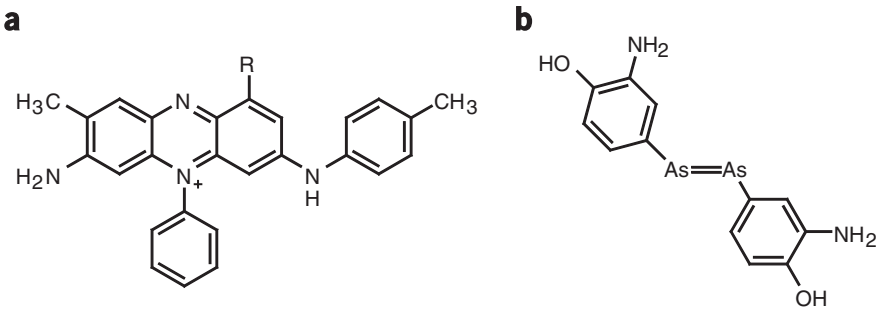


Figure 2 Structures. (**a**) Mauveine (R = mixture of CH_3 and H). (**b**) Salvarsan. Although it was structurally characterized only recently[13], mauveine sparked a nineteenth-century revolution in chemistry and chemical biology. Discovered by Paul Ehrlich, Salvarsan demonstrated the efficacy of the magic bullet approach to treating disease.

Contemporaneously, Swiss biochemist Friedrich Miescher (1844–1895) took the first concrete steps toward the eventual discovery of the double helical structure of DNA by James Watson and Francis Crick. Interested in the substructure of the cell, Miescher focused on the identification of proteins in the nucleus. Miescher made the practical, though slightly unpleasant, decision to use human leukocytes readily available in copious quantities from the pus-soaked bandages of a nearby surgical clinic. After working out conditions to separate intact cells from the bandages, Miescher next devised a procedure to isolate their nuclei, through treatment with warm alcohol to remove lipids of the plasma membrane, followed by proteolytic digestion of the cytoplasm with pepsin and sedimentation of intact nuclei. Using chemistry to advance biology, Miescher analyzed the contents of his purified nuclei with the chemical tools of the day—elemental analysis, digestion by various proteases and solubility in various solutions. In 1869, he recorded the following in a lab notebook (translated from German):

> In the experiment with the weakly alkaline fluids, I obtained, by neutralization of the solutions, precipitates which were insoluble in water, acetic acid, very dilute hydrochloric acid, or sodium chloride solutions; consequently, they could not belong to any of the known albuminoid substances. Where did this substance come from?[18]

Miescher called this substance "nuclein" and found that its elemental composition included not only the usual assortment of carbon, hydrogen, oxygen and nitrogen of known organic chemicals but also, surprisingly, phosphorus. Miescher's use of chemistry to initiate the faint beginnings of molecular biology did not cause the sensation that one might expect for such a key advance. Indeed, publication of Miescher's exciting results was delayed by the editor of the first biochemistry journal, Ernst Felix Hoppe-Seyler, who insisted on repeating and verifying the experimental results. Although many in the field disputed his discovery, Miescher continued to use chemical methods to unravel the mysteries of the cell. Miescher's student, Richard Altmann, coined the term "nucleic acid" to more accurately describe nuclein in 1889 (ref. 19).

The explosion of research at the chemistry-biology interface continues to the present day. The field remains driven by emerging technologies, such as microarrays, molecular display libraries, single-molecule techniques and combinatorial biosynthesis. Many current chemical biologists emphasize the use of small molecules to control cellular processes[20]. This approach to chemical biology would be familiar to its earliest practitioners, such as the magic bullet proponent, Paul Ehrlich. Similarly, using chemistry to enhance imaging has been a longstanding interest of chemical biologists from Anna Atkins onward. Of course, much has changed since the nineteenth century, from the analytical tools to the addition of powerful molecular biology techniques.

In summary, although the term would not be coined for at least a century, the roots of our field can be found in both biological and chemical experiments that today would clearly be classified under the heading of chemical biology. Examining history uncovers other interesting trends. First, several prominent early chemical biologists staked out controversial, public positions in the political debates of the day. Though their views were quite unpopular at the time, such courage illustrates the role leading-edge scientists can play in the national discourse. For example, many contemporary chemical biology experiments make use of *in vitro* molecular evolution, and could offer a useful counterpoint to the ongoing debates over teaching evolution. Second, our present considerably advanced state of knowledge in chemical biology did not emerge from a smooth arc of progress. In fact, serendipity played a key role in several key advances cited here. Third and most importantly, the historical record and current studies show the effectiveness of the chemical biology approach for advancing both chemistry and biology.

BOX 1 EXCERPT FROM *THE MOUSE'S PETITION*

OH! hear a pensive captive's prayer,
For liberty that sighs;
And never let thine heart be shut
Against the prisoner's cries.
For here forlorn and sad I sit,
Within the wiry grate;
And tremble at th' approaching morn,
Which brings impending fate.
If e'er thy breast with freedom glow'd,
And spurn'd a tyrant's chain,
Let not thy strong oppressive force
A free-born mouse detain.

—Anna Laetitia Aikin Barbauld

Aikin, A.L. The mouse's petition in *Poems* (Joseph Johnson, London, 1773). Reprinted online in *Romantic Circles* (Vargo, L. & Muri, A., eds.). Accessed 15 November 2005 (http://www.rc.umd.edu/editions/contemps/barbauld/poems1773/mouses_petition.html/).

Paul Ehrlich (circa 1913) in his laboratory. Winner of the Nobel Prize (in 1908, which he shared with Élie Metchnikoff), Ehrlich contributed groundbreaking discoveries in several areas, including cell imaging with aniline dyes, development of the magic bullet concept and antigen-mediated immune response. Image © Wellcome Library, London. Used with permission.

ACKNOWLEDGMENTS
We thank G. Fenteany, R. Martin and other readers for their helpful comments.

1. Anonymous. *Nat. Chem. Biol.* **1**, 3 (2005).
2. Priestley, J. *Experiments and Observations on Different Kinds of Air* (Johnson Press, London, 1774).
3. Ready, K.J. *Eighteenth-Cent. Life* **28**, 92–114 (2004).
4. Hoover, S.R. *B. Res. Humanities* **81**, 9–27 (1978).
5. Wright, A.J. *J. Clin. Anesth.* **7**, 347–355 (1995).
6. Wöhler, F. *Poggendorff's Ann.* **12**, 253–256 (1828).
7. Wöhler, F. *Ann. Chim. Phys.* **37**, 330–333 (1828).
8. Cohen, P.S. & Cohen, S.M. *J. Chem. Ed.* **73**, 883–886 (1996).
9. Schaaf, L. *Out of the Shadows: Herschel, Talbot and the Invention of Photography* (Yale Univ. Press, New Haven, 1992).
10. Atkins, A.A. *Photographs of British Algae: Cyanotype Impressions* Vols. 1–3 (privately published, Halstead Place, Sevenoaks, 1843–1853).
11. Gribbin, J. *The Scientists: A History of Science Told Through the Lives of its Greatest Inventors* (Random House, New York, 2004).
12. Toulmin, S. & Goodfield, J. *The Architecture of Matter* (Univ. Chicago Press, Chicago, 1962).
13. Meth-Cohn, O. & Smith, M. *J. Chem. Soc. Perkin Trans.* **1**, 5–7 (1994).
14. Garfield, S. *Mauve: How One Man Invented a Color that Changed the World* (W.W. Norton, New York, 2000).
15. Ehrlich, P. *Arch. Mikr. Anat.* **13**, 263–277 (1877).
16. Schiller, F. *Clio Med.* **5**, 145–155 (1970).
17. Miescher, F. *Die Histochemischen und Physiologischen Arbeiten* (Vogel, Leipzig, 1897).
18. Miescher, F. *Hoppe-Seyler's Med. Chem. Unt.* **13**, 441–460 (1871).
19. Fruton, J.S. *Proteins, Enzymes, Genes: The Interplay of Chemistry and Biology* (Yale Univ. Press, New Haven, 1999).
20. Schreiber, S.L. *Nat. Chem. Biol.* **1**, 64–66 (2005).