The Westheimer Institute
for Science and Technology

Major research collaborations

Center of Excellence in Genomic Sciences
Massachusetts General Hospital
The Scripps Research Institute
University of Texas
University of Washington
NSF Chemical Bonding Center
NASA Astrobiology Institute
The Templeton Foundation

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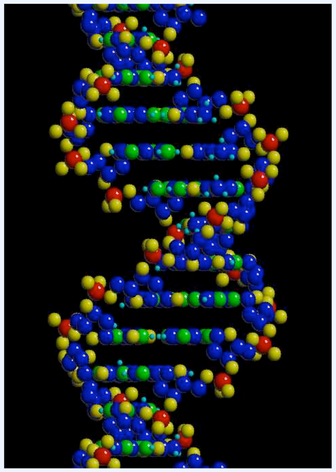
chemical genetics



geobiology

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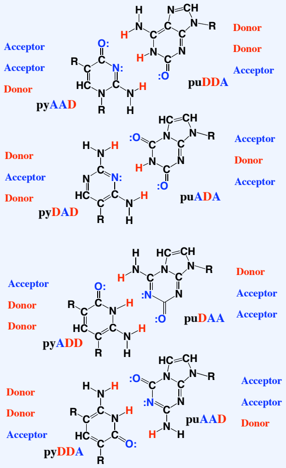
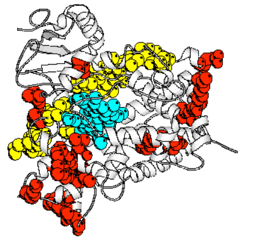
for Science and Technology

Joining molecular science, natural history, and medicine

synthetic biology

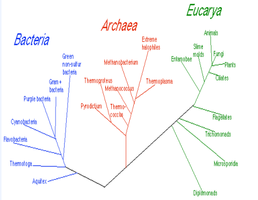


systems biology



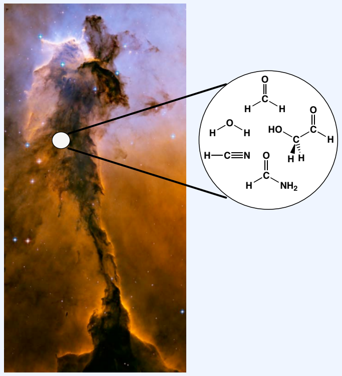
planetary biology

genomic biology

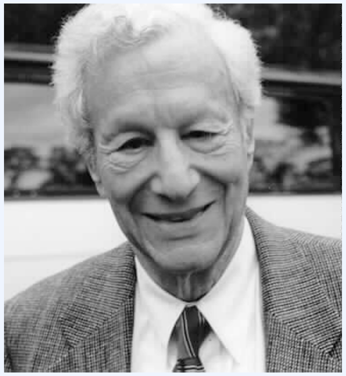


paleobiology

astrobiology



human biology



About Frank H. Westheimer

Frank Westheimer moved easily between chemistry, biology and computation long before it was fashionable. By doing so, he showed how polydisciplinarity generates discovery. Frank provides the inspiration for the polydisciplinary work done at the Institute.

Trained at Dartmouth, Harvard, and Columbia, Frank worked at the University of Chicago and Harvard. In his career, he developed three paradigms that today unify chemistry and biology.

First, Frank was an early practitioner of *physical organic chemistry*, which studies how chemical reactions occur. The reactions that he studied include those where molecules are oxidized or reduced, gain or lose phosphate, or release carbon dioxide.

Frank then turned to study the analogous reactions in biology. He began by seeking catalysis in amino acids, then metal ions, and then in enzymes themselves. His work encouraged the study of enzyme mechanism, which today is key to the development of pharmaceuticals and diagnostic tools.

Frank also introduced computation to molecular science. He founded *molecular mechanics*, and did the first computational studies of organic acids and bases. Today, molecular mechanics is key to all biological computation.

As with those of other generalists of the last century, Frank's contributions are so fundamental that it is difficult to believe that they were resisted when they were introduced. "Tierchemie ist Schmierchemie" (biochemistry is messy chemistry) was the view of German chemists who surveyed the mixing of biology with chemistry.

Modern society has benefited from science that is done without such blinders. Frank in 2003 asked where "our blind spots are now?" The Institute works to identify and remove these. We hope to have the same impact in the next century as Frank had in the last.

Westheimer, F. H. (2003) Reflections. *J. Biol. Chem.* **278**, 11729

A new organization for basic and applied research

The modern university as we know it may not be the most important developer of research and technology in the coming millennium. Its collegiate and departmental divisions are well recognized barriers to innovation and multidisciplinarity. Its governance hinders technology transfer. The Westheimer Institute has constructed an innovative organizational structure to match its innovative science, and to meet the needs of research in science and technology in the new millennium.

The Westheimer Institute is a part of the Foundation for Applied Molecular Evolution

Education for the 21st Century scientist

Themes in 21st Century science

The Institute faculty offer tutorials on topics that are not often found in formal graduate programs in the sciences, but which are critical for professional performance in science in the 21st century.

Fund raising: Funding is the key to successful science. Institute trainees have their skills in this area developed in both formal and informal settings.

Intellectual property and technology transfer: In the future, pioneering scientific research will need to rely less on peer review mechanisms, and more on return from technology that it generates. Institute trainees each submit a patent application which they prosecute *pro se*,to learn how this process works.

Verbal presentation: The key to successful scientists is the ability to convey scientific ideas verbally, to students, peers, and the public. Every lecture at the Institute is recorded, so that trainees can review their performance with the aid of coaches.

Outreach: A key to successful science is contact to the public. Institute trainees are involved in ongoing outreach activities ranging from elementary schools to the adult population, and also in activities that measure the success of outreach using quantitative metrics.

Creative thinking: Much of modern training in science avoids issues as basic as logic and creativity. Institute trainees are involved in both formal and informal programs to enhance skills in both areas.

Technology transfer

Technology developed by Institute scientists supports commercial products in many industries.

Bayer Diagnostics
EraGen Biosciences
Bristol-Myers Squibb
bioMerieux
Firebird Biomolecular
Alantos
Gilead
Eurogentec
Glen Research
Firebird Biomoleclar Sciences

Graduate studies at the Westheimer Institute

Outstanding professional competence. Graduate students receiving their Ph.D. at the Institute select a specific craft in which to build an *outstanding professional competence*. This places them in the top 10% of individuals at the same professional level in this craft. Depending on their choice, the student is apprenticed to the appropriate member of the Institute faculty:

Area	Faculty
Software engineering	Dr. Chamberlin
Synthetic organic chemistry	Dr. Hutter
Enzymology and protein chemistry	Dr. Benner
Molecular biology	Dr. Carrigan
Genetics and molecular evolution	Dr. Gaucher

Polydisciplinarity. Graduate students receiving their Ph.D. at the Institute are also expected to have *outstanding undergraduate competence* in each of the following areas.

Area	Faculty
Philosophy of science	Dr. Carrigan
Structure theory in molecular science	Dr. Hutter
Geology and paleontology	Dr. Benner
Mathematical analysis in science	Dr. Chamberlin
Cellular and organismic biology	Dr. Gaucher

Course work

The Institute faculty offer tutorials for credit for enrolled graduates, students, postdoctoral fellows, and visiting scientists.

Courses

Mathematical logic, modeling and analysis
Organic reaction mechanisms
Enzymatic reaction mechanism
The history of the cosmos, the Earth and its biosphere
Metabolic pathways and their regulation
Eukaryotic genetics and cell biology
Organization of biological systems
Evolutionary biology and molecular evolution
Medical genetics
Modern problems in human disease, diagnostics, and therapeutics

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Pioneering science

Synthetic biology. If you understand life, you should be able to re-create it. Institute scientists founded *synthetic biology*, which recreates emergent properties of living systems by constructing artificial systems. Together with Harvard and Scripps, the Institute hosts one of four Chemical Bonding Centers funded by the National Science Foundation, committed to developing this new field.

Systems biology. Genetics always acts within a complex biological setting.. Institute scientists work as part of a Center of Excellence in Genomic Sciences funded by the National Institutes of Health. The Institute develops tools to enable *systems biology*, quantitatively analyzing the biomolecules from biology. These tools today help improve the care of some 400,000 patients annually living with infectious diseases.

Genomics. With funding from the National Institutes of Health, the Institute works to improve genome sequencing and re-sequencing tools, offering the potential of *personalized medicine* based on genetic analysis., and ways to understand the human genome sequence.

Paleogenetics. Any system, natural or synthetic, is better understood if one understands *both* its structure *and* its history. Institute scientists invented the field of *paleogenetics*, which resurrects ancestral genes from ancient organisms for laboratory study. This adds experimental substance to historical narratives that join chemistry with biology.

Planetary biology. Life on Earth has evolved together with the planet and the cosmos; each cannot be understood without understanding the others. Institute scientists work with scientists at University of Washington as part of the NASA Astrobiology Institute to understand life from the molecule to the cosmos.

Chemical genetics. One goal of chemical genetics is to manipulate biological systems using small molecules. Institute scientists invented *dynamic combinatorial chemistry*, which allows a type of natural selection to be used to create biologically active small molecules. This tool is used today in pharmaceutical companies to generate new therapies.

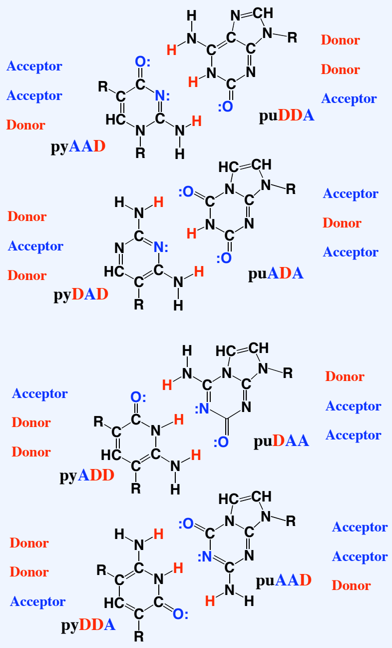
The origin of life and extraterrestrias. One longstanding problem in biology asks how life began. With support from the NASA Exobiology program and the Templeton Foundation, Institute scientists use their understanding of chemical reactivity, natural history, and planetary science to build models for how the first genetic systems took hold on Earth, how genetic systems might appear in alien life living on other planets, and what features of the life we know are universal.

Synthetic genetics and synthetic biology

The ability to synthesize is a test of understanding rooted deeply in molecular science. Nearly 20 years ago, Institute scientists began a program to understand molecules central to genetics by synthesizing new backbones and nucleobases for DNA and RNA.

This led to the first artificial genetic system, having 12 genetic letters instead of the 4 in natural DNA. Institute scientists have now combined organic synthesis, enzymology, and molecular biology to generate a molecular biology to support this artificial genetic system, showing that is can support Darwinian evolution.

Piccirilli, J. A., Krauch, T., Moroney, S. E., Benner, S. A. (1990) Extending the genetic alphabet. Enzymatic incorporation of a new base pair into DNA and RNA. *Nature* **343**, 33-37



A synthetic DNA with 12 genetic letters

A new field: Synthetic biology

Institute scientists are credited as founders of *synthetic biology* as a field. This field recreates the emergent properties of living systems using artificial molecular architectures. Institute scientists have joined scientists from Harvard and Scripps in a Chemical Bonding Center funded by the National Science Foundation. This team is committed to developing artificial genetic systems capable of Darwinian evolution.

Benner, S. A., Sismour, A. M. (2005) Synthetic biology. *Nature Rev. Genetics* 6, 533-543

Synthetic biology in the clinic

Alternative genetic systems support diagnostics tools that improve the health of 400,000 patients each year worldwide, helping physicians provide personalized care to manage infections by the HIV and hepatitis B and C viruses.

Bain, J. D., Chamberlin, A. R., Switzer, C. Y., Benner, S. A. (1992) Ribosome incorporation of non-standard amino acids into a peptide through expansion of the genetic code. *Nature* **356**, 537-39

Benner, S.A. (2004) Understanding nucleic acids with synthetic chemistry. *Acc. Chem. Res.* **37**, 784-797

The RNA world first?

In 1962, Alex Rich suggested that life began with catalytic RNA. A decade ago, Institute scientists combined chemistry and genomics to produce a model for the RNA world.

Benner, S. A., Ellington, A. D., Tauer, A. (1989) Modern metabolism as a palimpsest of the RNA world. *Proc. Nat. Acad. Sci.* **86**, 7054-7058

Colemanite, a borate mineral that stabilizes ribose

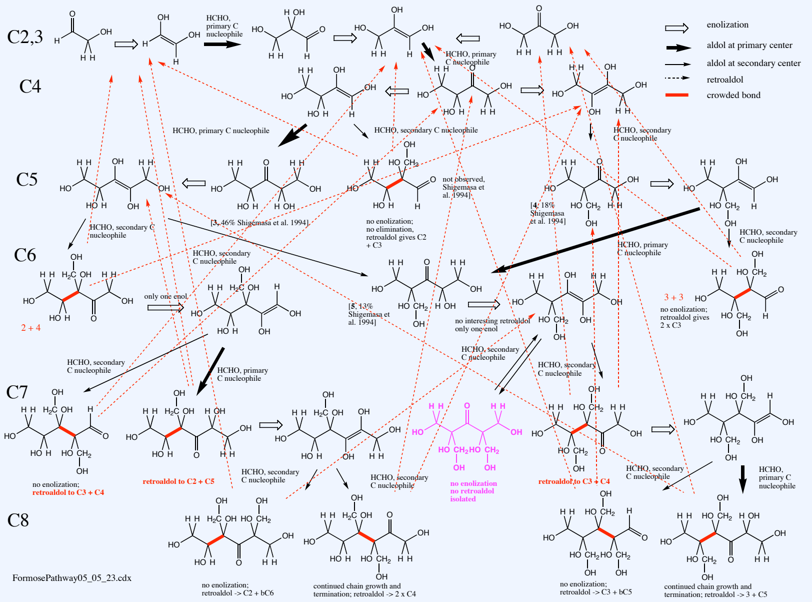
Origin of life

Did RNA support the first life on Earth? Institute scientists have joined the geology of borate minerals with mechanistic organic chemistry to suggest “yes”.

Ricardo, A., Carrigan, M.A., Olcott, A.N., Benner, S.A. (2004) Borate minerals stabilize ribose. *Science* **303**, 196

Physical organic chemistry and the origin of genetics

The Institute laboratories use mechanistic chemistry to understand how life might have originated on Earth, with a model that has the appropriate complexity (shown below).

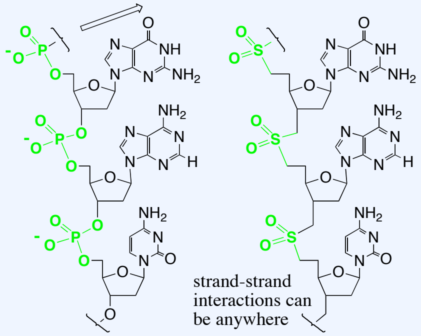


As simple as possible, but not simpler. A scheme showing possible paths for the formation of carbohydrate on early Earth.

Exobiology and alien genetics

How might alien genetics be recognized? NASA missions to Mars, Titan, and elsewhere make this no longer an academic question. Institute scientists do Earth-based research to inform NASA in its search for life in the galaxy.

Many forms of alien life have been conceived by science fiction writers. Which are reasonable?



strand-strand interactions can be anywhere

Second generation models for DNA

The repeating charge in the backbone of DNA and RNA has been regarded as an inconvenience. Synthetic biology at the Institute has shown that this feature is a key to molecular recognition in DNA, and may be a universal for life in the cosmos.

Benner, S.A., Hutter, D. (2002) Phosphates, DNA, and the search for nonterrean life: A second generation model for genetic molecules. *Bioorg. Chem.* **30**, 62-80

Organic compounds on Mars

The 1976 Viking mission reported no organic molecules on Mars. Institute scientists applied organic reactivity and planetary science to predict structures for Martian organic molecules. These may support human habitation on Mars.

Weird life

While most focus on water as a solvent for life, water is one of the scarcer fluids in the solar system More abundant is supercritical dihydrogen-helium mixtures (gas giant planets), liquid dinitrogen (Triton), and ammonia-water eutectics (Titan). Institute scientists serve on a panel of the National Academy of Sciences to define the limits of organic life in the cosmos.

Benner, S. A., Ricardo, A., Carrigan, M. A. (2004) Is there a common chemical model for life in the universe? *Curr. Opinion Chem. Biol.* **8**, 672-689

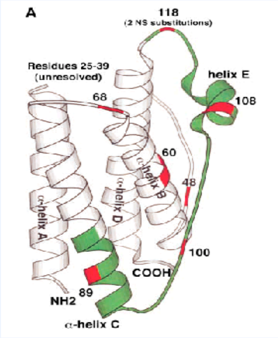
Bioinformatics and computational biology

Institute scientists were the first to do an *exhaustive matching* of a modern protein sequence database, and constructed one of the first bioinformatics workbenches. They were also the first to generate a *naturally organized genome sequence database*. Dr. Stephen Chamberlin, now at the Institute, led the software engineering team that converted this to a commercial product that was placed in the pharmaceutical industry.

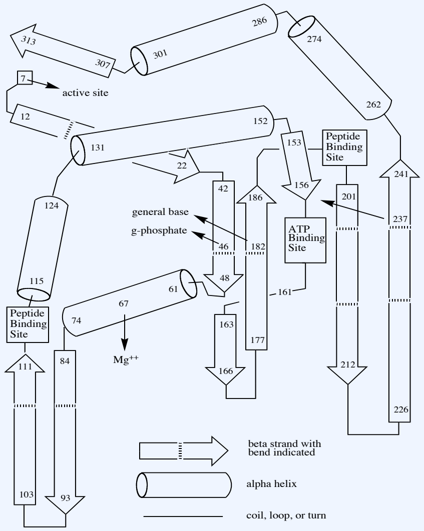
Gonnet, G. H., Cohen, M. A., Benner, S. A (1992). Exhaustive matching of the entire protein sequence database. *Science* **256**, 1443-1445

Evolution holds the key to protein folding …

The toughest problem in protein science was recast when Institute scientists showed that it was possible to predict the folded structure of a protein by analyzing its divergent evolution. In a feat called "a major breakthrough", the fold of protein kinase, was successfully predicted *de novo* in 1990; many successful predictions have followed.



Evolutionary bioinformatics helps understand the adaptation of the obesity protein leptin (2003)



The predicted structure of protein kinase (1990)

…and biomolecular function

When set in the context of natural history, protein sequence evolution also informs about protein function. Led by Eric Gaucher, Institute scientists develop new tools to detect when the function of a protein changes during evolution, and genetic changes that cause disease.

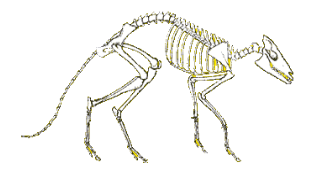
Benner, S.A., Cannarozzi, G., Chelvanayagam, G., Turcotte, M. (1997) *Bona fide* predictions of protein secondary structure using multiple sequence alignments. *Chem. Rev.* **97**, 2725-2843
Benner, S. A., Chamberlin, S. G., Liberles, D. A., Govindarajan, S., Knecht, L. (2000) Functional inferences from reconstructed evolutionary biology involving rectified databases. An evolutionary approach to functional genomics. *Research Microbiol.* **151**, 97-106

Joining chemistry with natural history

Any system, natural or man-made, can be better understood if one understands *both* its **structure** *and* its **history**. Yet molecular science has been largely separated from natural history in the modern academy. One mission of the Institute is to fuse the physical sciences with natural history, making it largely unique in academic research institutions.

A new field:
Experimental paleogenetics

Institute scientists were the first to **resurrect ancestral genes** from ancient organisms for study in the laboratory. Paleogenetics puts experimental data be-hind historical narratives that provide a heuristic understanding of "function" in biological systems. For example, resurrected proteins from ancient ruminant digestive tracts showed the evolution of ruminants adapting to global climate change.



A digestive enzyme of *Diacodexis*, which lived 40 million years ago, was resurrected to understand the connection between biomolecular physiology and a changing environment.

Jermann, T.M., Opitz, J.G., Stackhouse, J., Benner, S.A. (1995) Reconstructing the evolutionary history of the artiodactyl ribonuclease superfamily. *Nature* **374**, 57-59

At what temperature did bacteria live 3 billion years ago?

Structure of a bacterial elongation factor; one over 3 billion years old was resurrected for study in the lab.

Astrobiology asks about our most distant ancestors, including bacteria that lived three billion years ago. Institute scientists resurrected proteins from bacteria of that antiquity, and showed that these were optimally active at 65 °C. This suggests that bacteria near the root of the eubacterial tree were thermophiles.

Gaucher, E. A., Thomson, J. M., Burgan, M. F., Benner, S. A. (2003) Inferring the paleoenvironment during the origins of bacteria based on resurrected ancestral proteins. *Nature* **425**, 285-288

Natural history and human disease

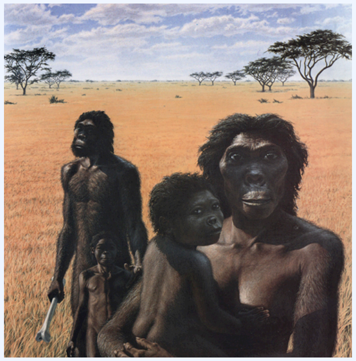
An Old World pig shortly after large litters emerged

A problem in modern genomics is that there is too much of it. Institute scientists encountered this when they were approached by researchers in pig reproductive biology. Pigs have three genes to convert testosterone to estrogen; one would seem to be enough. Combining computation, geology, paleontology, physiology, and genetics, Institute scientists built a hypothesis that these helped pigs have large litters.

Gaucher, E.A., Graddy, L.G., Simmen, R.C.M., Simmen, F. A., Kowalski, A.A., Schreiber, D.R., Liberles, D.A., Janis, C.M., Chamberlin, S.G., Benner, S.A. (2004) Planetary biology of cytochrome P450 aromatase from swine. *BMC Biology*. **2**, 19

The new field of planetary biology

Human biology is also shaped by changing environment in a changing planet. 60 million years ago, the ancestors to modern humans lost the gene to make vitamin C, presumably because they inhabited a fruity rain forest rich in the vitamin. But then, geological events led to the cooling and drying of the planet, and the loss of much of the rain forest. Humans left the vitamin C-rich forest, acquired the disease scurvy, and then lost another gene, allowing urate to accumulate. Urate replaces the antioxidant vitamin C, but causes gout. Further misadaptation is involved in obesity, diabetes, and hypertension.



Human disease is dominated by incomplete adaptation of human ancestors to a change in their environment, diet, and lifestyle.

Planetary biology and cancers

The prostate emerged in the lineage leading to modern humans about 150 million years ago. With it came a disease cluster associated with an incompletely adapted tissue, including prostate hyperplasy and prostate cancer. Retracing the natural history of prostate helps us understand the diseases of the tissue.