American Chemical Society AMA: I am M.G. Finn, Editor-in-Chief of ACS Combinatorial Science, here to discuss why combi chem is not dead. Ask me anything!

AmerChemSocietyAMA [1] and r/Science AMAs[1]

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Abstract

Welcome! I am M.G. Finn, Editor-in-Chief of ACS Combinatorial Science. My group does research in a variety of areas that seek to develop molecular function, but we define "molecular" in ways that go from small molecule drugs to large multiprotein assemblies to organisms. In particular, we develop and optimize reactions for bioconjugation and release, engineer virus-like nanoparticles for immunology, cell targeting, and enzyme encapsulation, and work on new ways to evolve aptamers and enzymes. Since moving to Georgia Tech in 2013, we are also doing a lot more materials science, trying to apply some of our click chemistry techniques and attitudes to the creation of new functional polymers and surfaces. An appreciation for molecular function is what motivated me to steer the journal into expanded waters, while retaining a core commitment to the publication of good synthetic chemistry. ACS Comb. Sci. now publishes papers in a wide variety of areas in which functional structures are made, identified, or enhanced by combinatorial means. We also like to highlight methods — synthetic, analytical, and theoretical — by which function can be created and measured. Combinatorial biology, materials development, and drug development are all combinatorial chemistry in my view, and so the field is most certainly very much alive. Thanks VERY much to everyone who posted questions and comments - I had a great time and you gave me some good things to think about. (Hopefully, that feeling is mutual.) I look forward to the next AMA.

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Who said it was dead and why? Automated and combinatorial synthesis approaches seem to be increasing at an exponential rate.

What_Is_X

You mention here an important subject that is sometimes ignored in the academic community: the importance of automation (and, more generally, of instruments and analytical techniques). In many ways, combinatorial science is driven by enhancements in machines to a greater degree than some other areas of chemistry and biology. The history of the field could probably be written in this way: from plate readers to arrays to microfluidics; from NMR to mass spec to high-content imagers to.... you get the idea.

Along with new machines also comes a requirement for new ways to process and analyze data. Bioinformatics, driven by DNA sequencing, has led this field for many years now, but many of the same kinds of techniques and algorithms are applied to combinatorial screening data, mass spectrometry, etc.

So, I never said combinatorial chemistry was dead....I agree that there's more going on than ever!

What are your thoughts on computational chemistry. Where do you think it hasn't been applied yet, or not applied correctly. What is the most new and excited area of comb. chem, or just chem, in your view?

dimkal

Computational (or "virtual") exploration of combinatorial space are now very common in the development of biologically active small molecules. Even large molecules are being predicted or analyzed in this way as computational approaches become ever more powerful.

These are important parts of the field. But, as always, they must be continually benchmarked and informed by experiment. The combination, when properly done, is extraordinarily powerful.

In my own work, we have found computation to be especially helpful in helping to explain why something happens (and therefore how to take the next step), rather than to predict the outcome ahead of time. I suspect this is generally true.

I work with antibiotic resistance, and the common discussion in the field is that combi-chem has failed as an antibiotic discovery strategy. Would you say this is fair? If so, why? What alternatives might work better? Is the "non-drug-like" nature of many antibiotics a challenge that can be overcome by employing different techniques?

superhelical

If, like me, you realize that the bugs do combinatorial chemistry/biology better than we do, then antibiotic resistance can be seen as a thumping victory for combinatorial science. We just happen to be on the wrong end of the stick.

Our response can occur on several levels. First, new drugs are being developed to fight drug-resistant pathogens by virtue of greater understanding of the molecular pathways available. Second, the ways in which pathogens evolve to meet a drug challenge can themselves be targets of therapeutic intervention. (In other words, attacking a bug's ability to evolve, as well as what it is evolving, is a viable option.) Third, can we create drugs that themselves evolve to meet an evolutionary challenge? Fantasy at the moment, but maybe not forever....

Your question of non-drug-like nature of antibiotics is a different matter. I don't believe that this property, however you define it, is responsible for the development of drug resistance. After all, everything evolves to meet challenges in its environment, most of them "natural" but no less damaging.

Hi Professor Finn! Thank you for doing this AMA.

I have always wondered if truly successful 'hits' are a commonplace in combi. chemistry. If so, how common do they occur? If not, are there any outstanding reasons for the difficulty of such a discovery?

Also, what is being done to improve any aspect of combinatorial chemistry?

I understand that the answers to my questions may vary across different fields and applications - If you can answer them according to your field of preference or just in a general context, I'd be grateful.

Thank you!

Motherofcurry

Hi, and you're very welcome. Thanks for participating.

There are lots of ways to answer your first question. Let's take drug discovery for a moment, and ask about the hit rate for the most generic kind of combinatorial effort - making random compounds and testing them for the desired activity. In that kind of "unbiased" situation, true hits are in fact quite rare. And how you do the experiment can make a lot of difference. But the measure of a combinatorial discovery project should not be the hit rate, but rather the quality of the hits (or leads), and what information the results give you about the system.

The field in general has learned some lessons, all of which are subject to change depending on the particular situation. Here are three (of many: (1) Greater diversity in compound structures are usually preferred in early experiments over greater numbers of similar structures. (2) Screening methods are of paramount importance, and should be designed to eliminate false positives (more important than missing true positives). (3) A well-designed combinatorial study should teach you something about your target even if you don't get a hit.

Other fields of combinatorial endeavor will have different lessons and hit frequencies. One of my favorites, biological evolution, doesn't even work this way, but it is inescapably powerful!

Thank you for taking the time to do this. There have been some nice relatively recent advances in Comi Chem screening to help with deconvolution, such as DNA-encoded libraries. I was wondering if there are new approaches you are particularly excited about, especially approaches currently in use by CRO-type companies. Thanks!

jdbatche

You hit on a very exciting one: DNA-encoded libraries are experiencing something of a surge in publications and activity in both academia and industry. (For those in the biz, I recommend the High Throughput Chemistry and Chemical Biology Gordon Conference -- there were lots of exciting developments discussed about DNA-encoding in the most recent of these meetings.)

Another personal area of excitement for me is the engineering of whole cells to report on the activity of test compounds, and on the next step, which is the performance to true evolution to develop molecular function. (As a simple level: create cells that make candidate molecules, and that live or die based on their function, or lack of function. If you do that, then you can harness evolution, rather than screening, do get functional structures. In principle, at least.)

Does combinatoric chemistry mean mixing shit together to see what happens? I've heard the term but never read into it.

Have microfluidic approaches to combinatorics been worthwhile, or just a gimmick?

iorgfeflkd

No, just mixing stuff together is unlikely to give useful results, and that is not what is meant by combinatorial chemistry. (Although I do not want to minimize how much fun it is to "mix shit together" - if you ask a bunch of chemists why they are chemists, you'll get a lot of answers that boil down to how enjoyable it is to make new things in this way....we just learn to do it better as we go along, I hope.)

Anyway, microfluidics provides an especially fast, precise, and useful way to mix things. And the easier it is to do the mixing (and analyze the result) the more tests one can do in a particular time. So while this might seem to enhance the value in "just mixing things," in combinatorial science we do this with a lot of thought up front about what gets mixed and why.

But your question does have a kernel of truth. The real power of combinatorial chemistry and the synthetic and analytical methods that go into creating this branch of science is that they allow you to do things that you can't think of. In other words, if I restricted myself to only those combinations of reagents that I knew gave a particular product in a particular way, I wouldn't learn anything. But if I try new combinations (in a well-thought-out way), I may find something unexpected, or find an unexpected way to accomplish a designed goal.

I'm not saying this as well as I would like to, but I hope I am transmitting the idea that surprise and information are the real coins of the realm in combinatorial science, in whatever field these techniques are applied...

Combi chem was popular in the chemical industry in the early 2000's, it was being applied every where from paint formulation to pharmaceuticals and catalyst design; millions of dollars was spent. But then not much came out of the effort.

What happened? Where did these efforts go wrong? Are the expectations more realistic now?

nallen

Another posted question is related: "What sort of developments have come out of combichem? Are there any currently marketed drugs, usable materials, or other widely available combichem-derived products on the market?"

I used the title "combi chem is not dead" in a somewhat tongue-in-cheek manner, but also because these questions are common. The initial efforts didn't go wrong - maybe people thought of them in too-rosy terms, but combinatorial approaches to drug discovery (the major initial area of use) are now so deeply ingrained in the field that they can be said to contribute to the large majority of research by companies in this space.

What has perhaps become better appreciated are the limits of combinatorial drug discovery as it was originally envisioned. To avoid a long (and very interesting) lecture, the basic lesson is that Biology is Complicated. Which leads to a very important corollary: the closer your screen is to the "real" application, the better.