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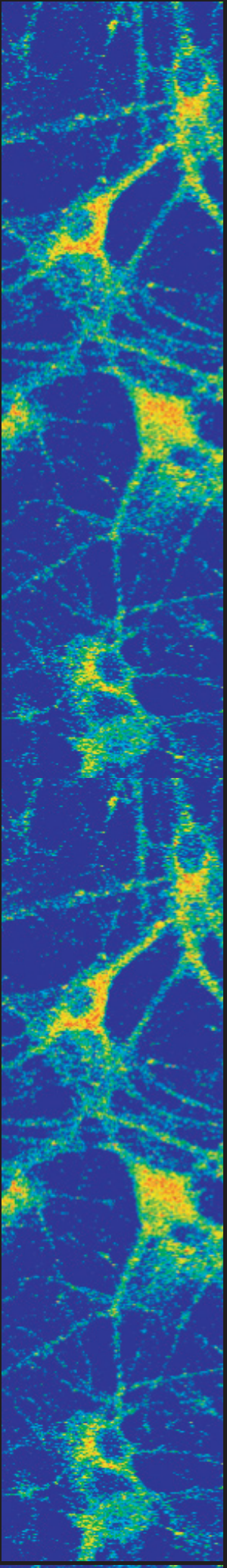
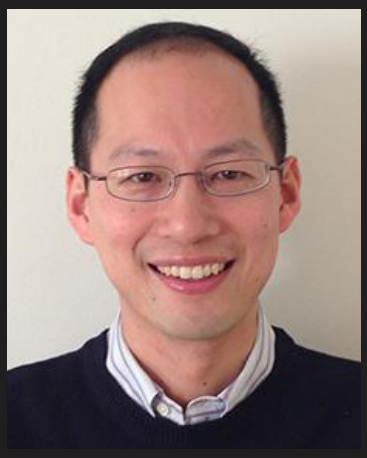


DETECTING SIGNALING ROLES OF TRANSITION METALS

Interview with professor Christopher Chang

BY JIARUI LIU, YU LUO, YANA PETRI, SASINAN SANGTEERASINTOP, JORDAN WONG, SOOHAN WOO, LAURA ZHU

Dr. Christopher Chang is a Professor of Chemistry and Molecular and Cell Biology at the University of California, Berkeley. He is also an investigator at the Howard Hughes Medical Institute. Professor Chang's laboratory is focused on the design and synthesis of chemical tools for molecular imaging, chemoproteomics, and optogenetics. In this interview, we talk about the detection of redox-active transition metals such as copper and iron by fluorescent probes and discuss their role in biological systems and disease.



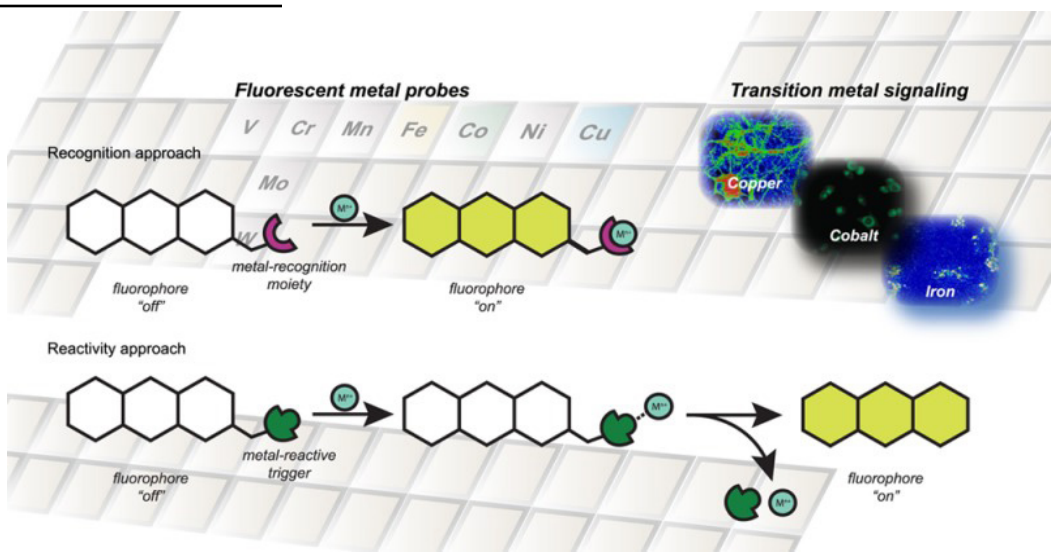
Professor Christopher Chang
[Source: UC Berkeley College of Chemis-

BSJ: How did you first get involved in research in the fields of Bioinorganic Chemistry and Chemical Biology?

CC: Bioinorganic Chemistry is a relatively new field of Chemistry, as it's in between the classic fields of Inorganic Chemistry and Molecular and Cell Biology. I did undergraduate research in Inorganic Chemistry and then graduate research in Energy Science and Inorganic Chemistry. As a postdoc, I started to get more interested into Chemistry/Biology interface. The research group we started at Berkeley pretty much became an amalgamation of the different sorts of chemistry experiences that I had up to that point.

BSJ: Redox-active transition metals have been largely thought of as static cofactors. What has inspired your interest in specifically studying cell signaling of labile transition metals?

CC: We view the periodic table as Nature's Rosetta Stone. When you look at everything around you, it's made up of combinations of different elements, and so is life. At slower time scales, you sustain life through metabolism; at faster time scales, you transfer information through signaling. We got interested in these faster time scales because it turns out that most people study long-term effects. You have to start from somewhere, however, because elements cannot be created or destroyed – only arranged in different combinations. We thus wanted to study the fastest and earliest time points of signaling



Recognition- and reactivity-based approaches for metal detection
[Source: "Recognition- and Reactivity-Based Fluorescent Probes for Studying Transition Metal Signaling in Living Systems"[1]]

to understand how it occurs. The term "labile" refers to something weakly bound, exchangeable, something that would move quickly. It turns out to be a view of continuum of elements and how they mix together.

BSJ: Your research group has developed novel fluorescent probes for studying the signaling roles of labile transition metals. What criteria must these probes meet to be suitable for imaging in living organisms?

CC: The most important thing is selectivity, because you want to distinguish different elements from each other. Selectivity is really the biggest challenge, because biology is very heterogeneous and very complicated. A human cell is different from a mouse or plant or yeast cell, or from a bacterial cell in your microbiome. Even within us, your brain is different from your liver; it's different from your skin, from your kidney, from your heart. And so the probe must be selective for a given context (e.g. specific cell type). The second important thing would be readout, or visual response from the probe, because we do imaging where changes in color relate to signaling.

"We design probes based on hard-soft acid-base theory, as well as shape selectivity or preferences for particular oxidation states"

BSJ: Your laboratory has pursued two general strategies for labile transition metal detection - "recognition" and "reactivity." What do these strategies encompass on a molecular level?

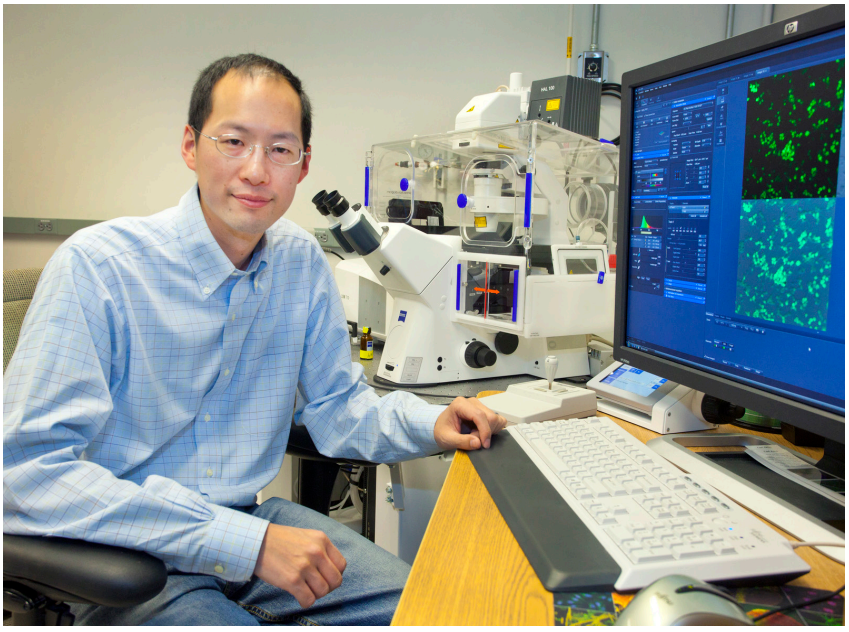
CC: The recognition approach is sort of the traditional approach. It goes back to the lock-and-key chemistry of enzymes. The element plays the role of the key and the probe plays the role of the lock. The idea of recognition is developing the right sets of locks to detect select element keys. The reactivity approach is sort of corollary to recognition – there are lots of keys that can fit in various locks. In the reactivity approach, the binding also causes some sort of chemical change. This gives you two filters of selectivity: not only binding, but also a reaction. Depending on the situation, we try one or the other.

BSJ: Several probes designed in your laboratory have been copper- or iron-specific. How do the probes differentiate between different oxidation states of these metals?

CC: That challenge makes the part of the periodic table we studied more difficult. We not only have elements, but also elements of different forms because they can attain multiple oxidation states. Our research goes back to the very fundamental principles of Inorganic Chemistry. We design probes based on hard-soft acid-base theory, as well as shape selectivity or preferences for particular oxidation states. For example, we can discriminate between Cu(I) and Cu(II) (note that Cu(I) is softer than Cu(II)) and so we can change a receptor or the reactivity group on the probe to suit the desired oxidation state.

BSJ: Why has your laboratory been so interested in studying copper? What role does this metal play in diseases like Menkes and Wilson's?

CC: One of the reasons why we study copper is that it is one example of a transition metal that is very abundant; also copper and iron are two major elements in biology that change oxidation states. The diseases that you mention turn out to be mainly genetic and are directly related to copper dysregulation. Patients with Menkes disease are copper deficient and have a genetic mutation centred in a specific protein. Wilson's disease, which runs in families, is the inability to pump copper out of liver. Copper builds up in liver and can't get to other parts of the body. Wilson's and Menkes diseases are models for more complicated neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's.



Using a fluorescent probe Copper Fluor-3, Professor Chang and his research group showed that copper signalling is essential to the health of the human brain[2]
[Source: Lawrence Berkeley National Laboratory]

BSJ: We noted that you have recently been involved in a project that aimed at creating a diagnostic tool for monitoring copper levels in biological fluids (such as blood). Could you please tell us a little bit more about this work?

CC: This work is a collaboration with Jeffrey Long's group.[3] Jeff is developing porous materials for energy applications like carbon capture. What we decided to do is see if we could use them for biological diagnostics or for environmental applications. The first concept was making a sponge, a selective sponge for copper that you could dip into bio-fluids and then selectively remove or take up copper in that material. The "divide-and-conquer strategy" refers to having a sponge to remove or being able to separate copper out in situ before adding any sort of imaging indicator. The indicator doesn't have to directly go into the bio-fluid; the colorimetric assay can be performed on the bench top or hopefully in some take-home test kit.

BSJ: Using Copper Fluor-3 sensor, you have recently shown that copper also plays an important role in neuronal function – it is a modulator of spontaneous activity in the brain. What are the advantages of this sensor?

CC: I would say that the one advantage of that sensor is that it allowed us to go from cells to tissue for the first time. It was really important for the neurobiological studies because you could isolate cells from brains and then make synaptic connections. The problem is if they're just in a dish, then those connection aren't natural. What you would really like to be able to do is dissect tissue where natural connections are made. That was the advantage of those types of probes. That allowed us to see what copper was doing in circuit that was natural and intact.

"One area that we are looking at is the brain and how metal signaling can dampen or control brain activity"

BSJ: We noticed that iron is another metal that your research group has been closely investigating. Why is it important to monitor labile iron pools? How does iron affect our health?

CC: Because it turns out that there is a certain amount of iron you need in your body. It is well known that you need it for respiration, electron transfer, oxygen binding and transport, as well as lots of metabolic types of oxidation, such as metabolizing food and drugs in your body. But it turns out that "static" iron doesn't account for all the iron that exists in your body. And so there's this other pool, which is called the labile pool, which has an unknown function. However, it is known to exist, because the metabolic proteins alone can't account for all the iron needed by the body. So one of the challenges is to actually see the labile pool, to see it changing over time.

BSJ: Probe metal-detection technology is now actively used in research. Does this discipline face any lingering limitations?

CC: Yes. It's a relatively new discipline, because it takes from a lot of different areas and isn't a classic field. I would call it "molecular sensing and imaging," because there is organic chemistry, inorganic chemistry, materials chemistry, chemical biology, and analytical chemistry. The limitations are that we don't really know how to selectively bind to or react with all the elements. There are over a hundred elements across the periodic table, and, so far, we only know how to work with less than a dozen really well. Rather than a limitation, however, I would call this more of an opportunity, because there all sorts of things - elements, length scales, tissues, animals, plants – to study and learn about. You could even do environmental sensing, such as in an ocean, or a lake, or the atmosphere.

BSJ: What are some of the future directions of your research?

CC: What we're interested in right now is looking at combinations of elements and how those give rise to behavior. A lesson we've learned is that a metal can serve as a signal, as well as a static cofactor, and it is just a matter of timescale. We have a whole region of time that we have analyzed in a basic way. One area that we are looking at is the brain and how metal signaling can dampen or control brain activity. An important question we've been led to is whether signaling controls certain behaviors. We're looking at sleep behavior, at regulation of fear, and at fight-or-flight responses. A paper we published this summer looks at your ability to burn fat, and that copper is necessary for proper fat burning. The idea is that you are what you eat, and transition metal signaling is controlling how much energy you burn. So the future direction of our research is investigating how signaling gives rise to behavior, rather than diseases, per say.

BSJ: Thank you very much for your time!

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