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# The Legacy of Ei-ichi Negishi: Eternal Optimism and Excellence

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Ei-ichi Negishi will remain known for pioneering and promoting the development of transition-metal catalyzed reactions in organic synthesis as well as fostering excellence and critical thinking among his collaborators. During his lifetime, with his wife Sumire by his side, he conquered many continents: in the chemical world, his name is associated with cross-coupling, cascade reactions, carbopalladation, zirconocene-chemistry and asymmetric synthesis; in life, we remember him as a kind, generous, and approachable individual that mastered golfing, singing, and skiing, among other things.

**Biography.** Born on July 14, 1935 in Manchuria as a Japanese citizen, Ei-ichi Negishi grew up in that region as a child before moving to Korea and, ultimately, to the Tokyo area of Japan, where he spent his high-school and university years. During this period of his life, he discovered skating, choir singing, and met his to-be lifelong beloved partner and wife, Sumire. Ei-ichi Negishi graduated from the University of Tokyo with a Bachelor's Degree in Engineering in 1958 and joined Teijin as a polymer chemist.<sup>1</sup> Thanks to a Fulbright scholarship, he moved to the United States in 1960 to undertake a PhD degree at the University of Pennsylvania, where he discovered physical organic chemistry and was exposed to the frontier of chemical sciences following seminars featuring many Nobel laureates including Prof. Herbert C. Brown among others. After graduation in 1963, he returned to Japan and reintegrated Teijin, but with his passion for chemistry, he decided to move back to the United States in 1966 to carry out a post-doctoral stay with the aforementioned H. C. Brown (Nobel Prize 1979) at Purdue University and became his assistant until 1972. There, he worked on organoboron chemistry, met Akira Suzuki (future co-listed Nobel Prize laureate), and developed for instance the chemistry of hexylborane. In 1972, he moved to the University of Syracuse (New York) as an assistant professor and was promoted to associate professor in 1976. There began his journey about transition-metal chemistry with the development of the cross-coupling reaction, focusing first on organozinc compounds and, palladium before exploring other organometallics (B, Al, Zr, etc.) and metal catalysts, in particular Ni. This is also the time when he discovered skiing, a sport that he practiced at good level his entire life (he especially enjoyed double diamond slopes in Vail or Squaw Valley in many instances with his group members). He then returned in 1979 to Purdue University as a full professor and continued the rest of his academic career there until his retirement in 2019. **His scientific career was devoted to exploring the chemistry of transition-metals as a mean to synthesize efficiently and selectively complex building blocks for organic synthesis, while training the next generation and passing on his passion for research and the world.** He was awarded the Nobel Prize of Chemistry in 2010 for his pioneering contribution to the field of cross-coupling. This prize was shared with Profs. Akira Suzuki and Richard F. Heck in recognition of the impact of their chemistries on the efficient synthesis of drugs, agrochemicals, and polymers. During his career, Prof. Negishi also made several additional landmark contributions that focused on assembling complex molecules via Zr- and Pd-catalyzed reactions, highlighting the power of organometallic

chemistry in the field of organic synthesis. His work was reported in ca. 400 publications and recognized in numerous awards and accolades: J. S. Guggenheim Memorial Foundation Fellowship (1987), Chemical Society of Japan Award (1996), ACS Awards in Organometallic Chemistry (1998) and Creative Work in Synthetic Organic Chemistry (2010), and Alexander von Humboldt Award (1998 – 2001) to name but a few. He was an elected member of the American Academy of Arts and Sciences (2011) and of the National Academy of Sciences (2014).

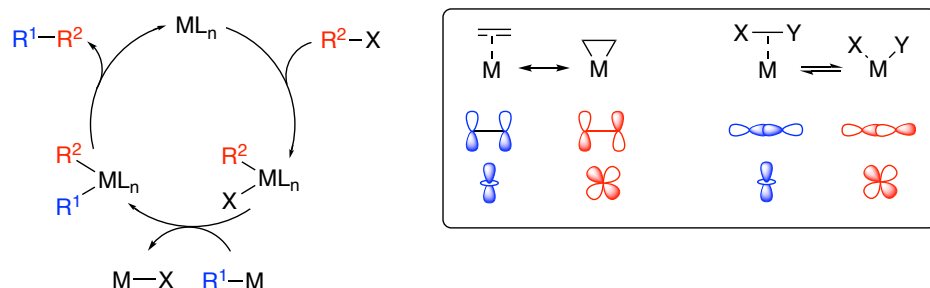
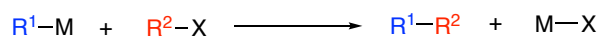


Pictures i) Prof. Negishi in the laboratory – 1982 (courtesy: Purdue Chemistry Archives), ii) Sumire and Ei-ichi Negishi in Stockholm – 2010 (courtesy: Purdue University).

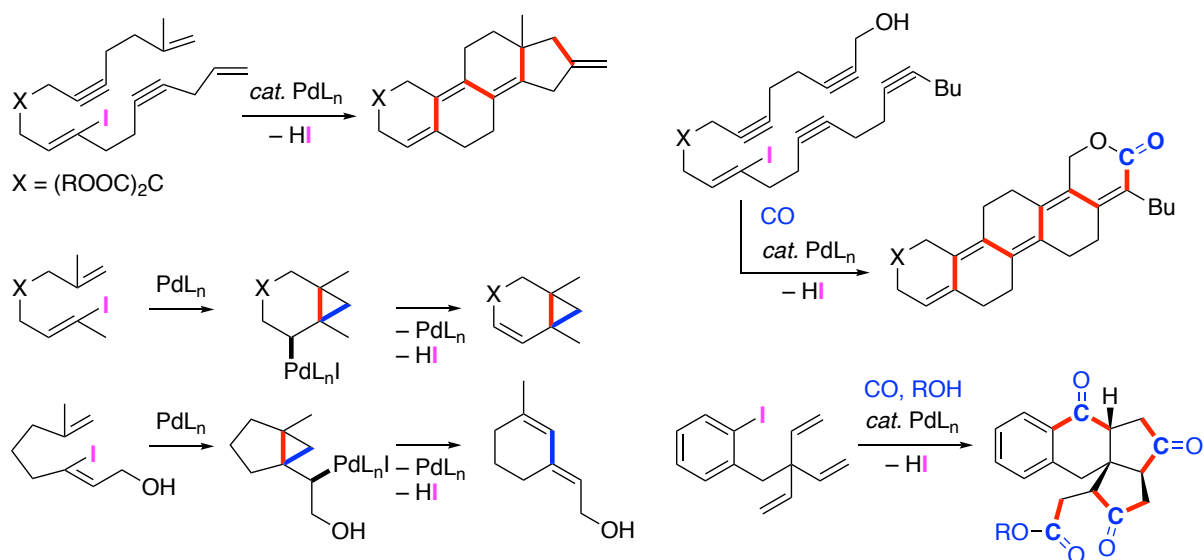
**Discovery of a new continent: Transition-metal catalysis.** The knowledge of the work of Ziegler and Natta from Negishi's background in polymer chemistry combined with his exposure to the work of several Nobel Laureates (including, at that time future Nobel Laureate and collaborator Prof. Herbert C. Brown), while studying at the University of Pennsylvania, certainly influenced his future work and his desire to explore transition-metal catalysis. Early in his career, following his contributions in organoboron chemistry with H.C. Brown, someone he deeply respected and admired, he made a pioneering contribution to cross-coupling while being an assistant professor, where he showed that palladium and nickel complexes could efficiently catalyze the formation of carbon-carbon bonds from stable organohalide ( $R-X$ ) and organometallic ( $R^2-M$ ) compounds. This simple concept enables the building of complex molecular structures via a "LEGO" game-like approach, as it was referred by Negishi himself. A far broader range of electrophiles and nucleophiles could be used beyond what was typically done at the time; while  $SN_2$ -reactions are by and large limited to  $sp^3-sp^3$  coupling, transition-metal catalyzed cross-coupling opened the possibility for  $sp^i-sp^j$  ( $i, j = 1, 2, \text{ or } 3$ ) coupling in a stereoselective manner when applicable, hence its potential and power in organic synthesis.<sup>1,2</sup> This chemistry is probably best illustrated with the synthesis of many vitamin intermediates, where the *E,Z*-stereochemistry in olefins needs to be fully controlled. These early works aroused his interest in exploring new (chemical) continents: (1) palladium chemistry to build

multiple carbon-carbon bonds in series using carbopalladation and carbonylation reactions to generate a high level of complexity – polycyclic structures – from linear acyclic chains in one step, and (2) organozirconium chemistry that ultimately led him to converting a Ziegler-Natta-like polymerization catalyst into enantioselectively building the carbon-carbon bonds of natural products and vitamin motifs, which is discussed in more details in the next two sections.

A)



B)

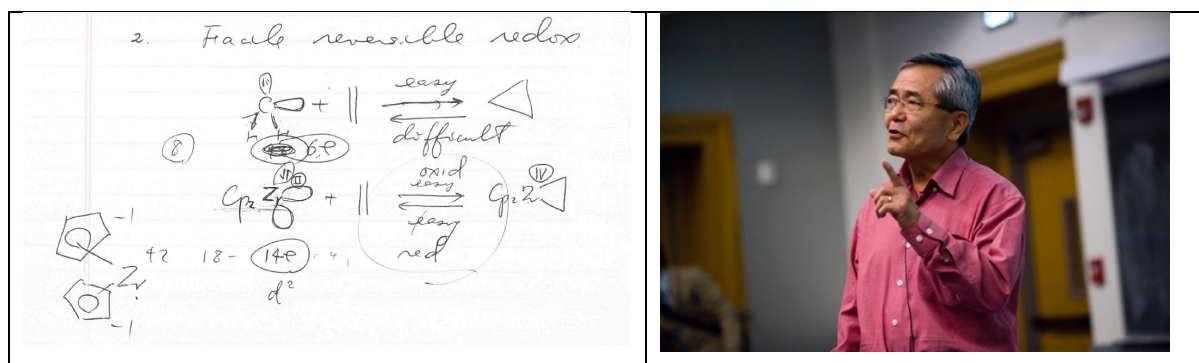


**Scheme 1.** (A) Early days, cross-coupling and orbital symmetry concept. (B) Exploration of cascade reactions (e.g. zipper-mode cyclisation) via sequential carbopalladation and/or carbonylation.

**Carbopalladation, carbonylation, and zipper-reactions.** Negishi's work on cross-coupling, the related Heck reaction, and (in all likelihood) his background in polymer chemistry led him to explore how one can exploit the insertion of an alkyne into a palladium-carbon bond to build complex molecules by carrying out multiple insertions in sequence to create carbon-carbon bonds while avoiding termination ( $\beta$ -hydrogen elimination) yielding polycyclic molecules from linear precursors. The most emblematic example is the one-step conversion of a linear molecule via a so-called “zipper” reaction to provide the ABCD rings of cholesterol-like molecules using alkyne moieties as relay functions, complementing the Johnson annulation process.<sup>3,4</sup> Moving from alkynes to 1,1-disubstituted alkenes as relay functions provided access to [3.1.0] and [4.1.0] bicyclic structures (containing a cyclopropane unit) or involved them as intermediates in the apparent “endo-mode” cyclization, ultimately leads to inversion of stereochemistry of the olefin relay

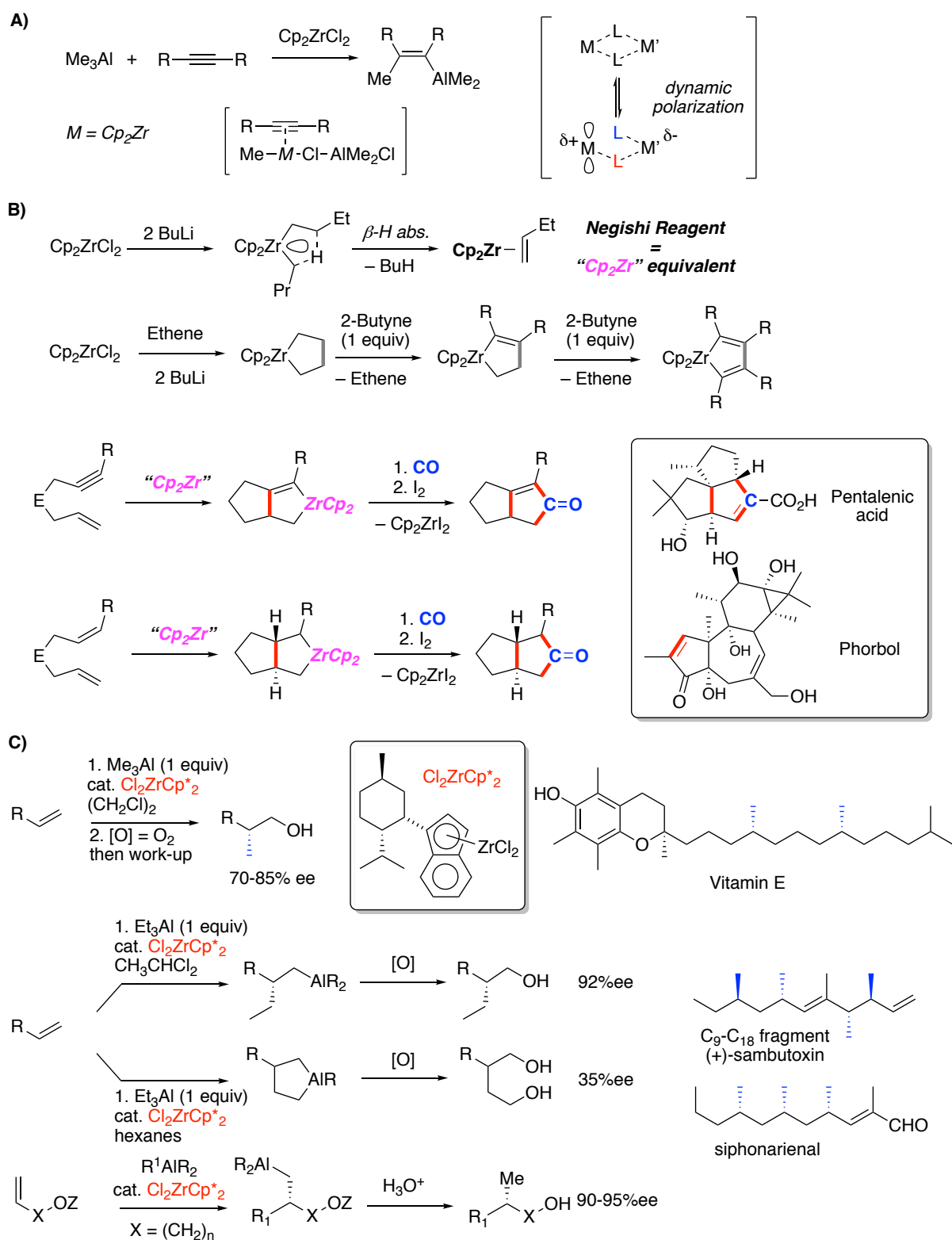
function—illustrating the fine balance between  $\beta$ -hydrogen/alkyl transfer/insertion in this chemistry.<sup>5</sup> Combining this reaction with carbonylative conditions enables the creation of very complex structures, with up to 7 carbon-carbon bonds made in one step, thus installing multiple stereocenters, carbonyl groups, and ester functionalities.<sup>6,7</sup>

**From fundamental organozirconocene chemistry to the Negishi reagent and zirconium-catalyzed asymmetric carboalumination of alkenes (“ZACA”).** The need for the full stereocontrol in alkenyl derivatives to complement cross-coupling approaches for the stereoselective synthesis of alkenes was certainly fueling his interest in organozirconocene and organoaluminium chemistries, hence Prof. Negishi’s early work on the carboalumination of alkynes.<sup>8</sup> Here, he showed that two metals can work in synergy to generate “super-electrophiles”; he would in fact often state “two is better than one”.<sup>9</sup> His interest in this topic led him to discover the so-called “Negishi” reagent<sup>10,11</sup> and to carry out detailed mechanistic studies on for instance the Dzemilev reaction, which showed the importance of  $\beta$ -H abstraction as a key elementary step in catalysis with zirconocene derivatives. The “Negishi” reagent, this putative 14-electron species that formally has two empty orbitals and a lone pair, was applied to enynes and opened up new ways to carry out Pauson-Khand-like reactions and to build very complex molecules such as pentalenic acid or phorbol as illustrative examples.<sup>11,12</sup> Applied to dienes, this enabled the formation of the unusual [3.3.0]-bicyclooctanones with a *trans*-stereochemistry and showed that metallacyclopentanes can be viewed as mere resonance structures of di-olefin complexes.<sup>13</sup>



iv) Left: an extract of the minutes of the discussion between Prof. Negishi and one of the co-authors, F. L. (every meeting with Prof. Negishi was documented and shared between the correspondants). Right: Prof. Negishi giving his undergraduate class just after being informed he was a recipient of the Nobel Prize of Chemistry—(Credit: Purdue University).

Ultimately coming back to a reaction closely related to the Ziegler-Natta polymerization, Negishi developed a stereoselective synthesis of  $\beta$ -substituted alkyl-alkanols that required the stereocontrolled single insertion of an olefin into a metal-carbon; this effort took years because of fast competitive insertion reaction or  $\beta$ -hydrogen elimination processes observed for most metallocenes. Exploiting the bulky Erker-ligand was key to its ultimate success<sup>14,15</sup> and enabled the stereoselective introduction of alkyl groups for a broad range of organic skeletons and the access to many complex natural products via a simple iterative approach.<sup>1</sup>



**Scheme 2.** (A) Carboalumination. (B) The “Negishi”-reagent and the chemistry of Zirconocene. (C) Zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA) and applications.

**Ei-ichi Negishi beyond chemistry: The French connection and a source of inspiration to us all**

Prof. Negishi kept strong personal and professional connections with his native country. Over the years, many Japanese scientists, from academia or industry, spent time in his laboratory, including longer stays for some of them as post-doctoral researchers. Among them, one can cite the case of Dr. Tamotsu Takahashi, who worked on the zirconium project at Purdue University then started his own academic career in Japan (where he is currently at the University of Sapporo), keeping strong scientific ties with Negishi. In fact, some of us had the chance to work there as part of scientific exchanges. Ei-ichi Negishi was proud of his Japanese culture and enjoyed sharing it with us—we were fortunate that he discovered our interest for Japanese food, which led us to go for group lunch many times at Heisei, a very good Japanese restaurant (yes, in Lafayette); our Polaroid pictures were still posted on the wall of the restaurant the last time some of us could go and check—it was in 2011 to celebrate the Nobel Prize of Prof. Negishi. Another country that had developed a strong relationship with Purdue University and the Negishi laboratory is France. Indeed, one may wonder at this stage why these “French” co-authors decided to write a text devoted to the Legacy of Prof. Negishi. In fact, most of the co-authors—F.C., D.C., C.C., F.L., J.L.M., and C.R.— come from the same undergraduate and master’s study program (CPE Lyon [Ecole Supérieure de Chimie Physique Electronique], which was called ESCIL [Ecole Supérieure de Chimie Industrielle de Lyon] at the time before its fusion with another school of chemistry in Lyon) and were fortunate to carry out their PhD or post-doc with Prof. Negishi ca. 20 to 30 years ago. CPE Lyon was a pioneering engineering school in France that sent more than 50% of their students to study and/or do a one-year internship abroad to validate their master’s degree, already in the late seventies. The intricacies of the French education system made it difficult to integrate graduate school programs in the United States at the time—a pioneering director of CPE Lyon (Y. Bonnet) was able to convince several American universities of the value of the French students, thus opening the possibility for us to join the graduate program of the Chemistry department of Purdue University among others. CPE Lyon, which had Victor Grignard as a former director and Yves Chauvin (Nobel Prize of Chemistry 2005 for his work on metathesis) as an alumnus, had a strong focus on industrial chemistry combining organic chemistry and chemical engineering, with fundamental chemistry. The school taught us as well foreign languages and project management, and a number of disciplines. We had the chance to have outstanding instructors in organic chemistry and catalysis, Prof. Goré and Malacria, only to name a few, who always presented and explained the latest development, even in an undergraduate curriculum. They also involved us, students, to present contemporary research literature or how large-scale processes worked (which was quite an unusual educational concept at the time). Moving from Lyon, the astronomy capital of France, to Lafayette, IN in the mid-eighties and nineties was certainly a change of lifestyle for all of us. However, the peaceful and beautiful Purdue campus (and the Japanese restaurant discussed above) as well as the proximity of Chicago (with Chicago Cubs baseball team, blues bars, and museum) were certainly an asset and ideal place to focus on our PhDs! Our training in organic chemistry, catalysis and transition-metal chemistry made Ei-ichi Negishi’s laboratory, a natural place to carry out a PhD. Working with Prof. Negishi was a blessing: **observing him thinking out loud and**



witnessing his thought process taught us a lot about how to raise critical questions early in a project and how to always seek simplification. The point was never to carry out experiments “to fill-in in tables” but rather to carefully design experiments to answer well-posed scientific questions and to demonstrate the generality (the shortcoming and/or the elegance) of the approach. While critical, honest and frank, Prof. Negishi was always accessible and offered genuine feedback, building confidence into oneself as well as inviting introspection. We all remember the “See me, please— EN” Post-it notes stuck on our notebook at the desk (close to our wooden bench and the row of hoods), indicating that an important scientific discussion about the latest results was about to take place and new potential directions could emerge. **Prof. Negishi often reminded us that (chemistry) research is like the exploration of new (chemical) continents: one has to be prepared, eyes wide open, ready to continue or change the course of action, and keeping our ultimate goal in mind and a fresh spirit – eternal optimism.** Each of us also remember memorable times at conferences—whether it was being challenged at golf, ping pong, skiing or singing karaoke. Prof. Negishi was an advocate of work/life balance; he was opened up to art and sport, encouraging us to excel in whatever we do. Years later, one can see his impact on our way of thinking and managing. He was a true mentor, transmitting his work ethic to his collaborators as well as his passion for chemistry and research. Some of us went to industry and understood later the real impact of his work. The thrill to discover, invent, and bring innovative solutions stays with us forever; all of us hope to carry on his concept of happiness, eternal optimism, and excellence.



**Pictures** iv) Left: Prof. Negishi golfing (Credit: Negishi Family), v) Top right: The French crew (the three on the left: F. L., C. C., and D. L.) during the visit of Prof. J. Huet (right; in charge of international relation at CPE Lyon) together with Prof. H.C. Brown and E. Negishi (center)—1992. Credit: F. Lamaty. Bottom right: Prof. Negishi, friends, and former collaborators (the picture includes C.C., F.C., and J.L.M.) during

a symposium organized at Purdue University—2000. Credit: Purdue University).

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