tribute

A tribute to the Philadelphia Lipid Group on the occasion of their retirement

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On October 21, 2013, many in the lipid research community gathered to mark the retirement of four of its most recognizable and accomplished colleagues: George H. Rothblat, Michael C. Phillips, Sissel Lund-Katz, and Margarita de la Llera-Moya (**Fig. 1**). These scientists formed the core of what is colloquially known as the Philly Lipid Group and were responsible for one of the longest standing Program Project Grants (PPGs) in the lipid field, originating at the Medical College of Pennsylvania (MCP) and concluding at the Children's Hospital of Philadelphia (CHOP). The Symposium, entitled "Advances in HDL Structure and Function" was held at the Abramson Research Center at CHOP and was attended by 130 former trainees, collaborators, and friends from across academia and industry. The presentations echoed the wide breadth of research centered in the group over its 37-year history, encompassing the details of lipoprotein structure and cutting-edge assessments of lipoprotein function, and finishing with the therapeutic use of peptides and recombinant lipoproteins against atherosclerosis. The symposium was organized by Dan Rader and supported by CHOP, CSL Behring, Resverlogix, and Vascular Strategies.

A BRIEF HISTORY OF THE PHILLY LIPID GROUP

In 1976, Julian Marsh (a leader in the study of lipid metabolism) was the Chair of the Department of Physiology and Biochemistry at MCP. With a desire to build a strong focus in lipidology, he recruited a young George Rothblat from the University of Pennsylvania. Trained by the great David Kritchevsky, Rothblat was doing pioneering work on cholesterol metabolism using a novel method called tissue culture (1). At MCP, Rothblat joined Jane Glick and graduate student Margarita de la Llera (Moya) to study the interactions of lipoproteins with cultured cells, including some of the earliest descriptions of neutral lipid ester accumulation in "foam cells" upon exposure to extracellular lipoproteins. With big plans to attain a critical mass for a program project grant, Marsh (a physiological biochemist) and Rothblat (a cell biologist) realized they needed a physical chemist to round out the group's expertise. At the IVth International Symposium on Atherosclerosis in 1976, a chance meeting—in a bar—between Rothblat and Graham Shipley solved this problem. Shipley suggested that the group contact his former Unilever colleague and squash partner Michael Phillips. Phillips had been a postdoc in Buffalo, NY with James Danielli and Alan Cadenhead (leading figures in the membrane field) and was working in the Biophysics Division at Unilever Research Laboratories in the UK. No doubt tired of the English weather, it turned out that he was interested in returning to the States. Even before Phillips' arrival at MCP in 1978, the three successfully applied for a PPG from the NHLBI entitled "Biology of Atherosclerosis" in 1977. The addition of postdoctoral fellow turned junior faculty member, Sissel Lund-Katz, added expertise on the use of nuclear magnetic resonance (NMR) to study the structure and dynamics of lipid and, eventually, protein molecules in the plasma lipoproteins. Under Dr. Marsh's leadership, the PPG was renewed in 1982 with a continued focus on a highly multidisciplinary and multisystem approach to understanding lipoprotein metabolism and its impact on atherosclerosis. In 1984, the leadership of the group transitioned to Rothblat who oversaw another PPG renewal in 1987. During this time, the group played a major role in helping to shape the *Journal of Lipid Research*, as both Marsh and Phillips served as Editors-in-Chief from 1983 to 1986. Also, during the 1980s, the group underwent considerable expansion with the addition of Ed Fisher and his programs on apoB and LDL/VLDL secretion and lipid hydrolases, Kevin Williams with an interest in how proteoglycans mediate ligand uptake and degradation in cells, and Mahmood Hussain and his studies on chylomicron metabolism, among others. There were also significant interactions with the Nutrition Research Division of the Department led by Catharine Ross, Earl Harrison, and colleagues. In 1991, the chairmanship was passed to Phillips who oversaw additional PPG renewals in 1992 and 1997. It was during this time frame that MCP became part of the rapidly expanding Allegheny Health, Education, and Research Foundation (AHERF), which, at its peak, consisted of 14 hospitals and two Philadelphia medical schools, MCP and Hahnemann, which AHERF merged in 1994. In the largest nonprofit healthcare failure in history

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Fig. 1. The honorees. From left to right: Michael Phillips, Margarita de La Llera-Moya, Sissel Lund-Katz, and George Rothblat.

to that point, AHERF declared bankruptcy in 1998, leaving the combined medical school with an uncertain future. Despite this turmoil, the science ongoing in the Lipid Group was as strong as ever. With some members of the group striking off on their own, Phillips, Rothblat, de la Llera-Moya, and Lund-Katz moved the core of the PPG across town to CHOP in 2000. Here, they joined forces with former MCP medical student/student researcher, Dan Rader, located across the street at the University of Pennsylvania. With Rader adding a robust human clinical dimension to the ongoing PPG, they renewed the grant two more times in 2003 and 2008. With the close of this 7th cycle of the PPG, the core individuals who have been with the program since its inception have elected to retire in November (**Fig. 2**).

CONTRIBUTIONS TO SCIENCE

These four individuals are responsible for nearly 450 peer-reviewed scientific publications related to lipid and lipoprotein metabolism. This number increases substantially when one considers the many additional investigators associated with the group over its history. Many of these reports laid the foundation upon which much of our current understanding of lipidology is built. The early work of Rothblat, Glick, and de la Llera-Moya represents some of the first applications of tissue culture technology in the lipid field, providing a mechanistic framework for the uptake of lipoproteins by cells and the pathological consequences of how the lipids are handled and stored intracellularly (2, 3). Additionally, the group is widely credited with founding the field of cholesterol efflux studies. The combination of Phillips' understanding of lipid/water interfaces with Rothblat's insight into cellular lipid movement led to one of the first detailed mechanistic descriptions of the efflux of cholesterol from cells in the early 80s (4, 5). The group produced many studies that define the characteristics of cellular donors and lipoprotein acceptors that drive the process widely known as the classic aqueous diffusion model. They were also among the first to recognize the potential of cyclodextrins as cholesterol acceptors from cells, providing the field with an important research tool and potential treatment strategy (6). Throughout the 1990s, there was significant debate as to whether cholesterol efflux proceeded primarily through aqueous diffusion or was mediated through 'apolipoprotein-mediated' mechanisms as argued by leaders like Jack Oram, Shinji Yokoyama, and others. With the discovery of the ABCA1 transporter's role in cholesterol efflux, it became clear that both modes of efflux were important and the Philadelphia group played key roles in defining the magnitude of these different pathways in different cell types (7). They also characterized the role of SR-BI as a protein facilitator of the aqueous diffusion pathway (8) and used synthetic peptides and full-length apolipoproteins to derive the 'membrane microsolubilization' mechanism for apolipoprotein-mediated cholesterol efflux (9). This concept underpins the popular Phillips model of ABCA1-mediated cholesterol efflux in which apolipoproteins are postulated to interact with and stabilize the transporter to create a strained membrane structure that allows the apolipoprotein to solubilize cell surface lipids (10). More recent studies defined how the composition of the cell membrane dictates the size distribution of ABCA1-generated HDL particles (11). Rothblat and de la Llera-Moya's years of work measuring the transfer of cholesterol from cultured macrophages to both mouse and human plasma laid the foundation for larger scale clinical studies aimed at assessing HDL 'quality versus quantity'. This led to the seminal collaboration with Rader and colleagues showing that the cholesterol efflux capacity of apoB-depleted human plasma is a more robust indicator of cardiovascular disease protection than the classic clinical measure of HDL cholesterol levels (12). Vascular Strategies, a biotechnology company specializing in functional assessment of HDL, was spawned from the group based in part on these advances. The work done in the group for many years on the biology of cholesterol-loaded cultured macrophages

Fig. 2. Alan Tall, Tilden-Weger Professor of Medicine at Columbia University, delivers a talk on the role of ABCG4 in cholesterol efflux and platelet production at "Advances in HDL Structure and Function", a symposium to honor the retiring Philadelphia Lipid Group.

also led to the development of the Rothblat/Rader reverse cholesterol transport (RCT) mouse model (13). Arguably the best characterized in vivo model of RCT, some variant of this method is currently used by most major groups studying atherosclerosis. The group also made critical contributions to the field of apolipoprotein structural biology. The work of Lund-Katz and Phillips defined the domain organization of apoE and apoA-I, leading to the most complete mechanistic scheme for apolipoprotein lipid binding available to date (14).

In addition to the considerable scientific contributions, the Philly Lipid Group also contributed immeasurably to the future of lipid research by training many of its current leaders. These four individuals alone have trained nearly 60 postdoctoral fellows and 25 PhD students now spread across the US, Canada, Europe, Japan, and Australia. Graduates of the program include professors in academia, physicians in clinical practice, scientists in most of the major pharmaceutical companies and several of the biotech companies, even biotech CEOs. In addition, numerous faculty members who have been part of the program over its history have gone on to become some of the foremost authorities in their areas of expertise.

Although these outstanding scientists are retiring from day-to-day laboratory science, they each plan to remain intellectually engaged in the lipid field while spending much deserved time traveling and being with family. As this chapter in the history of this influential group closes, their impact will continue to be felt for many years through the quality of their science and the continued success of their trainees. As one of those trainees, I speak for many in expressing my heartfelt appreciation for the wonderful scientific training that I received in the group and for the life-long support and friendships that I have enjoyed since leaving. I join the rest of the lipid field in congratulating Sissel, Maggie, George, and Mike on their accomplishments and wish them the best of luck as they take life a bit easier.

REFERENCES

1. Rothblat, G. H. 1977. Tissue culture in the study of atherosclerosis. *Adv. Exp. Med. Biol.* **82:** 707–711.
2. Glick, J. M., S. J. Adelman, M. C. Phillips, and G. H. Rothblat. 1983. Cellular cholesteryl ester clearance. Relationship to the physical state of cholesteryl ester inclusions. *J. Biol. Chem.* **258:** 13425–13430.
3. de la Llera, M., J. M. Glick, and G. Rothblat. 1981. Mechanism of triglyceride accumulation in rat preadipocyte cultures exposed to very low density lipoprotein. *J. Lipid Res.* **22:** 245–253.
4. McLean, L. R., and M. C. Phillips. 1981. Mechanism of cholesterol and phosphatidylcholine exchange or transfer between unilamellar vesicles. *Biochemistry.* **20:** 2893–2900.
5. Rothblat, G. H., and M. C. Phillips. 1982. Mechanism of cholesterol efflux from cells. Effects of acceptor structure and concentration. *J. Biol. Chem.* **257:** 4775–4782.
6. Kilsdonk, E. P., P. G. Yancey, G. W. Stoudt, F. W. Bangerter, W. J. Johnson, M. C. Phillips, and G. H. Rothblat. 1995. Cellular cholesterol efflux mediated by cyclodextrins. *J. Biol. Chem.* **270:** 17250–17256.
7. Yancey, P. G., A. E. Bortnick, G. Kellner-Weibel, M. de la Llera-Moya, M. C. Phillips, and G. H. Rothblat. 2003. Importance of different pathways of cellular cholesterol efflux. *Arterioscler. Thromb. Vasc. Biol.* **23:** 712–719.
8. de la Llera-Moya, M., G. H. Rothblat, M. A. Connelly, G. Kellner-Weibel, S. W. Sakr, M. C. Phillips, and D. L. Williams. 1999. Scavenger receptor BI (SR-BI) mediates free cholesterol flux independently of HDL tethering to the cell surface. *J. Lipid Res.* **40:** 575–580.
9. Gillotte, K. L., M. Zaiou, S. Lund-Katz, G. M. Anantharamaiah, P. Holvoet, A. Dhoest, M. N. Palgunachari, J. P. Segrest, K. H. Weisgraber, and G. H. Rothblat, et al. 1999. Apolipoprotein-mediated plasma membrane microsolubilization. Role of lipid affinity and membrane penetration in the efflux of cellular cholesterol and phospholipid. *J. Biol. Chem.* **274:** 2021–2028.
10. Vedhachalam, C., P. T. Duong, M. Nickel, D. Nguyen, P. Dhanasekaran, H. Saito, G. H. Rothblat, S. Lund-Katz, and M. C. Phillips. 2007. Mechanism of ATP-binding cassette transporter A1-mediated cellular lipid efflux to apolipoprotein A-I and formation of high density lipoprotein particles. *J. Biol. Chem.* **282:** 25123–25130.
11. Lund-Katz, S., N. N. Lyssenko, M. Nickel, D. Nguyen, P. S. Chetty, G. Weibel, and M. C. Phillips. 2013. Mechanisms responsible for the compositional heterogeneity of nascent high density lipoprotein. *J. Biol. Chem.* **288:** 23150–23160.
12. Khera, A. V., M. Cuchel, M. de la Llera-Moya, A. Rodrigues, M. F. Burke, K. Jafri, B. C. French, J. A. Phillips, M. L. Mucksavage, R. L. Wilensky, et al. 2011. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N. Engl. J. Med.* **364:** 127–135.
13. Weibel, G. L., S. Hayes, A. Wilson, M. C. Phillips, J. Billheimer, D. J. Rader, and G. H. Rothblat. 2011. Novel in vivo method for measuring cholesterol mass flux in peripheral macrophages. *Arterioscler. Thromb. Vasc. Biol.* **31:** 2865–2871.
14. Saito, H., P. Dhanasekaran, D. Nguyen, P. Holvoet, S. Lund-Katz, and M. C. Phillips. 2003. Domain structure and lipid interaction in human apolipoproteins A-I and E, a general model. *J. Biol. Chem.* **278:** 23227–23232.