2014 Curt Stern Award Introduction: Mark Daly[1]

Aarno Palotie[2,3,4,5,6,7,*]

It is a great pleasure to introduce my close friend and colleague Mark Daly, the 2014 recipient of the Curt Stern Award, which is presented yearly for outstanding scientific achievements in human genetics over the past decade.

David Altshuler recently told me the following: "If aliens were to invade the earth and humankind had to turn to one computational geneticist to figure out the alien DNA in order to save everyone, I'd want Mark Daly to defend us from the apocalypse."

David Goldstein, meanwhile, said this: "Mark is a deep and original thinker, honest beyond measure, fearless in interpretation, and one of the best people you will ever meet."

Indeed, we all know that Mark is smart, but the standard definition alone doesn't apply: he seems to be on a different planet. What is truly unique about him, however, is the fact that he can afford to be humble. He is that exceptional.

Mark grew up right outside of Boston and stayed in the area throughout school, university, and later, his career. He went to the Massachusetts Institute of Technology for his undergraduate degree, but not with aspirations to focus on genetics: his early top career choices were either professional poker player or lawyer (looking back, this might actually have been a useful combination). As a physics undergraduate, he chose to join Eric Lander's lab at the Whitehead institute—connections between this decision and a possible poker career are unclear.

Mark's fascination with data dates back to his early years in science. "Mark always leaves a dataset better off than how he found it," says Andrew Kirby, Mark's longtime colleague. Not much has changed in that respect: he still enjoys feeling immersed in raw data. If he is only dealing with higher-level data, he feels blind.

While diving into data in Whitehead, he also met his future wife, Mary Pat Reeve, now the mother of their four wonderful children. Their romance was sparked while they were staring at sequence data in monochrome monitors displaying gray dashes. In these monochrome monitors they, together with Jonna Hästbacka, found the diastrophic dysplasia mutation. Subsequently, their life would change from shifts of gray to full color and blossom.

Mark's team has developed or contributed significantly to the development of numerous methods that have become industry standards. Among these are GeneHunter, Haploview, PLINK, GATK, GRAIL, and DAPPLE. The leading philosophy of each of these methods has always being sharing, disseminating, and developing.

Mark's passion for developing new, modern tools that break boundaries does not seem fitting when one looks at the devices preferred by Mark himself: his personal gadgets are always a minimum of two versions behind. It took quite a bit of wrangling behind the scenes to get him an iPhone. It appears that progress sometimes needs a fine balance between keeping a foot in the past and reaching for the moon.

But, there is more to success than just sticking to the old while striving for the next scientific discovery. It's about being able to see what is immediate and what can wait and having the stamina to make decisions on these grounds.

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[2]Institute for Molecular Medicine Finland, University of Helsinki, 00014 Helsinki, Finland; [3]Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA; [4]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA; [5]Stanley Center for Psychiatric Research, Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA; [6]Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114, USA; [7]Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA
*Correspondence: aarno.palotie@helsinki.fi

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In spite of the fact that he once wished to become a lawyer, Mark displays a monumental dislike for administrative formalities. Sure, he doesn't get a kick out of filling out conflict-of-interest documents or reports—few of us do—but he does not even care about his own academic rank. Mark, who is among the ten most cited scientists in genetics and genomics and has produced 17 papers that have all been cited more than 1,000 times, has not bothered to apply for a full professorship at Harvard.

"It is too much administrative hassle. You have to bother so many colleagues to write uninteresting letters," he says. "We should concentrate on producing exciting results instead."

Pat Sullivan crystallizes this tendency as follows: "Mark simply cannot be bothered to do the self-promotion and self-aggrandizing that can typify some in the field. He would rather turn his formidable intelligence to the next major problem in genomics."

Mark has been the driving force in some of the most remarkable recent success stories of modern human disease genetics. Just to mention a few, he has led genome-wide association studies in inflammatory bowel disease and schizophrenia and been one of the pioneers in exome sequencing in neuropsychiatric diseases, most prominently in autism. He has led these large consortia with enthusiasm and good spirit, an appreciation and respect for his peers, and a passion to move the field forward.

As Mark has shown, being the statistical geneticist of our time is about enthusiasm, data, and joy of solving challenges. It is not about self-promotion or building defense barriers. It is also about setting priorities. One thing is even more important to Mark than science: his family. He is an excellent father—a fact confirmed by Mary Pat—and his office hours are worked around his schedule of dropping off and picking up his kids. He spends his weekends with their hobbies, minimizes his travel in order to not be away from home, takes holidays with his family, and whenever possible, takes his family with him when work-related travel takes more than a couple of days.

Yes, Mark is exceptionally smart—so smart that he can afford to be humble, joyful, giving, helpful, and devoted to his family life. He is a true model for the next generation of scientist.

As our mutual friend and colleague Ben Neale says: "Mark's sparkling intellect and imagination is only matched by his kind and caring nature. To possess either quality is rare, but to have both is truly unique."

2014 Curt Stern Award: A Tryst with Genetics[1]

Mark J. Daly[2,3,4,5,*]

> The future beckons to us. Whither do we go and what shall be our endeavor? … We have hard work ahead. There is no resting for any one of us till we redeem our pledge in full.
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> —Jawaharlal Nehru ("Tryst with Destiny")

I do not know which is the greater honor: the truly unexpected honor of being recognized by one's peers in The Society, for which I'm deeply grateful to the Awards Committee, or the indescribable honor that Aarno has just bestowed upon me with his introduction. At both I am left very nearly speechless.

By means of offering thanks to the numerous people without whom I certainly would not be standing before you, I'll start by giving a very brief glimpse into the activities that I've been privileged enough to be a participant in and that have led me to where I am. As a boy, I had always imagined the greatest vistas of science to be those of space—and then as the 1970s turned to the 1980s, microelectronics and computing. Without question, when I began at the Massachusetts Institute of Technology (MIT), these were the things that I figured to work on—certainly not biology, which, to be honest, hardcore MIT students in my day always considered a bit of a "softer" science.

But, as we know, both the world and our view of it are constantly changing.

At MIT, I was permanently hooked by the elegantly intertwined histories of genetics and statistics at a very young age when I was fortunate enough to join the brilliant Eric Lander as a summer student at a time when he was still learning biology and developing the foundations of quantitative trait locus and homozygosity mapping with David Botstein, linkage analysis with Phil Green, and the math of physical mapping and sequencing with Mike Waterman. Hanging around the Whitehead Institute and seeing these seminal ideas and papers forged could for me be described, to say the least, as "formative." And it was also at the Whitehead that I was to meet the only person who has had a greater influence on my career development—that person, of course, is my wife, Mary Pat.

I promise not to bore you with my personal history, and in order to keep to that, I'll move swiftly through the next periods of time. The first segment of my career was dedicated to delivering software and algorithms for every fresh problem in genome mapping. By the close of the 1990s, however, I had turned to applying the emergent tools of genomics to complex human disease in general and to Crohn disease and colitis in particular. This was really a transition point for me—although it was the mathematics and computational aspects of genetics that first drew me in, it is the mission that we could apply these in the service of medicine with an ultimate goal of improving human lives that has become my passion, as it is many of yours. What a privilege it is that this is what we get to do as our "job" every day.

The inflammatory bowel disease (IBD) work led to many unanticipated opportunities. The first came through pursuing one region of the genome at a time when we had no genome reference or next-generation sequencing (NGS) techniques and were still genotyping one SNP or simple sequence-length polymorphisms at a time (molecular dark ages to some of the younger of you). Through no more than looking for patterns while hunting for a first IBD-associated gene (with John Rioux and Tom Hudson), we came across some of the early evidence of the linkage-disequilibrium patterns that would drive the HapMap project, which would in turn lay the groundwork for the genome-wide association study (GWAS) era.

The HapMap Project began my long-term partnership with David Altshuler and Stacey Gabriel and with waves

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[2]Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, USA; [3]Program in Medical and Population Genetics and Stanley Center for Psychiatric Research, Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA; [4]Harvard Medical School, Boston, MA 02115, USA; [5]Institute for Molecular Medicine Finland, University of Helsinki, 00014 Helsinki, Finland
*Correspondence: mjdaly@atgu.mgh.harvard.edu

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of amazing statistical genetics colleagues around the world (including the man I'm sharing the podium with this morning), but more than this, it was in many ways a launching point in my career. I developed deep collaborations with international researchers—for whom I owe thanks not only for scientific mentorship and partnership but also for education on the responsibilities we take on when we accept the privilege of being medical genetics researchers. For this, as well as their amazing science, I am grateful to many, such as Aravinda, Leena and Aarno, Gert-Jan (who, along with Eric, also became my thesis promoter at Leiden), Leif, and the many Whitehead Institute faculty who were exceedingly generous mentors when there was nothing necessarily "in it" for them. It was also at this time that I was becoming a mentor, and although it is impossible to thank them all individually, the partnership with so many collaborators and skilled postdocs and trainees during this time is clearly most responsible for my being on this stage today.

Throughout the HapMap Project, we were building toward the idea of genome-wide association, although we knew we had to wait for technology and partnership to make this a reality. Although HapMap was hard work and gave us a framework, and I take no credit for the technological advances, it's really the ushering in of a new era of collaboration that I'm most proud to have been a participant in. Despite the fact that institute heads and promotion committees sometimes acted as though scientific credit was a zero-sum game, many looked past this and banded together in collaborations that, at least as far as genetics was concerned, were unprecedented in scale and in productivity.

The early work in IBD led me into ever-expanding collaborations to this day in the genetics of IBD; they have been remarkably instructive in moving us rapidly from the time we considered "complex" to mean perhaps five or ten genes to now having to wrestle with the numerical realities, functional interpretation, and translational opportunities of diseases with hundreds of contributing risk factors. For this I must acknowledge the partnership of the international IBD genetics community and my profoundly brilliant colleague Ramnik Xavier, with whom I work on the interpretation and translation of these findings.

Needing to fill a gap left by the end of HapMap—not to mention an acute unmet need in general—I've spent much of my last 10 years on the genetics of autism and schizophrenia, where we've seen really the most stunning progress, first with bona fide copy-number variations and rare mutations starting in autism and finally with GWAS in schizophrenia. I cannot overstate the role that collaborations such as the Psychiatric Genetics Consortium and the Autism Sequencing Consortium are having in this area, and the transformation of this field in recent years into one of optimism as incontrovertible proof has emerged that these diseases are medical, molecular, and potentially treatable has been breathtaking.

It has also been gratifying to have been able to help work out how our 1980s-style analytic thinking could be reapplied to the modern challenges of NGS processing, calling, and analyses. Moving from early brainstorming with Eric and others on the first output of next-generation sequencers to the Genome Analysis Toolkit to what Konrad presented this morning and to what is now possible for clinical genetics has been equally breathtaking. During these recent years, I have been blessed to work with so many additional fantastic trainees. I would be remiss not to say that when I asked for the opportunity to hire faculty, in my wildest dreams I could not have envisioned that two colleagues as brilliant and committed as Daniel and Ben would be willing to join this crazy enterprise. To watch them and their trainees flourish, and being recently joined by Aarno, is a gift that keeps on giving every day.

Myself included, we have as a community perhaps overused Churchill's "end of the beginning" quote to describe finally overcoming the first hurdle of gene identification in complex disease. I've recently come to think that a better analogy might be the transcendent speech delivered by Nehru on the eve of Indian independence—where in a singular celebratory moment, he chose to recognize both the enormity of the challenges that lay ahead and at the same time the true privilege it was to be in a position to take them on. This is really the message of this meeting—what has been accomplished is remarkable, yet we have so much more ahead of us if we wish to bring genetics full circle back to individuals. There are so many encouraging signs toward this end—collaborative community efforts to aggregate data and perform anonymous genetic "matchmaking" and other ways in which we can turn n of 1 into n of significance. The message of Cynthia and others this week has been that we cannot wait until absolute certainty to engage individuals and patients and that they will have a right to their genomes—whether for sharing, second opinions, or what have you. An instructive analogy may be drawn to the way medical imaging data are handled as we wrestle with how to engage patients while legitimate uncertainty and differences in interpretation might exist among experts.

In such a world, however, it is absolutely incumbent on us that we do a much better job of self-policing. We have learned over and over the importance of laboratory and statistical rigor in advancing genetic results to patients or genetic research findings to molecular biologists and chemists. In all cases, there is so much riding on our expert interpretation as geneticists. Now, all of us can interpret the 20^{th} mutation in a fully penetrant Mendelian condition or understand a univariate p value of 10^{-20} or apply Lander-Kruglyak linkage thresholds—but we have not yet learned how to amalgamate all available data to interpret rare variants in unknown genes, or outside genes entirely, and we certainly have not established a rigorous framework by which common or rare DNA variation can be turned into predictors of complex human diseases and phenotypes. We have confidence that the clinical genetics community

here, with their longstanding expertise, and efforts by the American College of Medical Genetics and Genomics, NCBI, and numerous others will move us in that direction. That said, the research community needs to resist the temptation to be a bit more fast and loose with rare mutations in the case where a good story fits, as it so often does.

At this time, we are also seeing waves of papers claiming the ability to predict common, often psychiatric, traits from GWAS data—and an even more disturbing trend that some of these are being directly marketed to clinicians—even while the claims are unvalidated and likely to be misinterpreted. Now, one could simply say that scientific process sorts these things out over time—but whether we embrace, or simply acknowledge the inevitability of, an era where individuals and patients are informed participants in their genome studies, we unquestionably need to be our own harshest critics. False connections between mutation and disease, and false predictions of devastating psychiatric conditions, have great power to damage—and rather than hope everyone does the right thing or wait for some governmental agency to regulate, we as a community and society should be proactive in tackling these issues.

If we're also serious about genetics as a first step in a long-term effort to rationalize therapeutic development, we need to embrace partnerships with industry—real efforts where partners across academia and industry are designing and interpreting studies together and sharing and releasing results to the fullest extent possible and where ideas and not simply dollars are changing hands. Certainly this requires some cultural shifts on our end as well as in the pharmaceutical industry. Our directors and promotion committees need to value these activities as critical to our ultimate mission and not as unimportant diversions. We also need to think of our training responsibility as not just filling the top universities and research hospitals but also providing the most skilled workforce to industry so that the entire workforce from basic discovery to delivery of new therapies is as expert as possible. We also need to be equally proud of trainees who commit to this path.

So, Nehru's call resonates with me, and I urge anyone I haven't put to sleep to think on it in this way. Without question, we are privileged to share a field that offers the remarkable opportunity to work at the cutting edge of science while engaged in an endeavor that has as its goal nothing short of the betterment of the human condition. Far more than this award today, it is the privilege of going to work every day that is the real award I've received in my life—excepting of course the greater and even less deserved reward I have every day of the five people sitting in front here. For them, for all our families, and for billions around the world, it's on us to deliver on the promise of genetics and genomics in this generation.

So my deepest thanks again go to The Society for this honor—and let's get back to work!