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Product Review

Science Translational Medicine – improving human health care worldwide by providing an interdisciplinary forum for idea exchange between basic scientists and clinical research practitioners

Science Translational Medicine – ein Forum für den interdisziplinären Wissensaustausch zwischen Grundlagenforschern und klinischen Forschungsärzten mit dem Ziel, die Patientenversorgung weltweit zu verbessern

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Abstract

Science Translational Medicine's [1] mission is to improve human health care worldwide by providing a forum for communication and interdisciplinary idea exchange between basic scientists and clinical research practitioners from all relevant established and emerging disciplines. The weekly journal debuted in October 2009 and is published by the American Association for the Advancement of Science (AAAS), the publisher of *Science* and *Science Signaling*.

The journal features peer-reviewed research articles, perspectives and commentary, and is guided by an international Advisory Board, led by Chief Scientific Adviser, Elias A. Zerhouni, M.D., former Director of the National Institutes of Health, and Senior Scientific Adviser, Elazer R. Edelman, M.D., Ph.D., Thomas D. and Virginia W. Cabot Professor of Health Sciences and Technology, Massachusetts Institute of Technology. The *Science Translational Medicine* editorial team is led by Katrina L. Kelner, Ph.D., AAAS.

A profound transition is required for the science of translational medicine. Despite 50 years of advances in our fundamental understanding of human biology and the emergence of powerful new technologies, the rapid transformation of this knowledge into effective health measures is not keeping pace with the challenges of global health care. Creative experimental approaches, novel technologies, and new ways of conducting scientific explorations at the interface of established and emerging disciplines are now required to an unprecedented degree if real progress is to be made. To aid in this reinvention, *Science* and AAAS have created a new interdisciplinary journal, *Science Translational Medicine*.

The following interview exemplefies the pioneering content found in *Science Translational Medicine*. It is an excerpt from a Podcast interview [2] with Dr. Samuel Broder, former director of the National Cancer Institute and current Chief Medical Officer at Celera. The Podcast was produced in tangent with Dr. Broder's Research Perspective "Twenty-Five Years of Translational Medicine in Antiretroviral Therapy: Promises to Keep", published in *Science Translational Medicine*, 7 July 2010; Volume 2, Issue 39 [3].

Dr. Broder's perspective marks the 25th anniversary of modern antiretroviral drug discovery and development. In the early 1980s, Dr. Broder's research team adapted the nucleotide analog AZT for treating HIV infection, thus ushering in the era of antiretroviral therapies that have enabled HIV-positive individuals to live longer. The Podcast interview was conducted by Annalisa VanHook, Associate Online Editor, AAAS.

Keywords: Science Translational Medicine, basic research, translational research, clinical research, emerging disciplines, interdisciplinary, human biology, AIDS, HIV, HTLV, disease, retroviruses, antiretroviral therapies, AZT, National Cancer Institute, immunodeficiency, cancer, translational medicine, pharmaceutical, new paradigms in medicine

Zusammenfassung

Science Translational Medicine [1] liefert ein Forum für den interdisziplinären Wissensaustausch zwischen Grundlagenforschern und klinischen Forschungsärzten aus allen wichtigen etablierten und aufkommenden Disziplinen, mit dem Ziel, die Patientenversorgung weltweit zu verbessern. Die wöchentliche Fachzeitschrift erschien zum ersten Mal im Oktober 2009 und wird von der American Association for the Advancement of Science (AAAS), dem Herausgeber von *Science* und *Science Signaling* veröffentlicht.

Die Fachzeitschrift bietet von Experten bewertete Artikel, Perspektiven und Kommentierungen und wird von einem internationalen Beratungsgremium angeführt, das unter Leitung des führenden wissenschaftlichen Beraters, Elias A. Zerhouni, M.D., ehemaliger Direktor der National Institutes of Health, und des leitenden wissenschaftlichen Beraters, Elazer R. Edelman, M.D., Ph.D., Thomas D. and Virginia W. Cabot Professor of Health Sciences and Technology, Massachusetts Institute of Technology, steht. Das Redaktionsteam von *Science Translational Medicine* wird von Katrina L. Kelner, Ph.D., AAAS, geleitet.

Die Wissenschaft der translationalen Medizin bedarf eines tiefgreifenden Wandels. Trotz der Fortschritte in unserem fundamentalen Verständnis der Humanbiologie und der Entwicklung leistungsstarker neuer Technologien in den vergangenen 50 Jahren, kann die rasche Umsetzung dieses Wissens in effiziente gesundheitliche Maßnahmen nicht mit den Problemen der globalen Patientenversorgung Schritt halten. Um einen wirklichen Fortschritt zu erzielen, benötigen wir jetzt, an der Schnittstelle etablierter und aufkommender Disziplinen, in einem nie dagewesenen Ausmaß, kreative experimentelle Ansätze, neuartige Technologien und neue Methoden zur Durchführung wissenschaftlicher Untersuchungen. Zur Unterstützung dieses Zieles haben *Science* und AAAS eine neue, interdisziplinäre Fachzeitschrift ins Leben gerufen, *Science Translational Medicine*.

Das nachfolgende Gespräch veranschaulicht den bahnbrechenden Inhalt, der in *Science Translational Medicine* gefunden werden kann. Es handelt sich dabei um einen Auszug aus einem Podcast-Gespräch [2] mit Dr. Samuel Broder, dem ehemaligen Leiter des National Cancer Institute und gegenwärtigen Chief Medical Officer von Celera. Der Podcast erfolgte in Anlehnung an Dr. Broders Forschungsperspektive „Twenty-Five Years of Translational Medicine in Antiretroviral Therapy: Promises to Keep“ (Fünfundzwanzig Jahre translationale Medizin in der antiretroviralen Therapie: Versprechen, die zu halten sind), die am 7. Juli 2010 in Band 2, Ausgabe 39 von *Science Translational Medicine* veröffentlicht wurde.

Dr. Broders Perspektive markiert das fünfundzwanzigjährige Jubiläum der Entdeckung und Entwicklung moderner antiretroviraler Medikamententherapien. Zu Beginn der achtziger Jahre stimmte Dr. Broders Forschungsteam das Nukleosidanalogon AZT auf die Behandlung von HIV-Infektionen ab, wodurch die Ära der antiretroviralen Therapien eingeleitet wurde, die HIV-positiven Patienten ein längeres Überleben ermöglichte. Das Podcast-Gespräch wurde von Annalisa VanHook durchgeführt, Online-Mitherausgeberin, AAAS.

Schlüsselwörter: Science Translational Medicine, Grundlagenforschung, translationale Forschung, klinische Forschung, aufstrebende Disziplinen, interdisziplinär, Humanbiologie, AIDS, HIV, HTLV, Krankheit, Retroviren, antiretrovirale Therapien, AZT, National Cancer Institute, Immundefizienz, Krebs, translationale Medizin, pharmazeutisch, neue Paradigmen in der Medizin

Twenty-five years of translational medicine in antiretroviral therapy: promises to keep

Interviewer – Annalisa VanHook: *Before HIV was identified as the causative agent of AIDS, and before HTLV-1 was identified as the causative agent of a subset of T cell lymphomas, researchers didn't seem to think it was likely that retroviruses would cause disease in humans. And even once HIV and HTLV were identified as causing disease, then people seemed to think that it might be futile to try and treat these retroviruses. Why was that idea prevalent in the scientific community?*

Interviewee – Dr. Samuel Broder: The existence of animal retroviruses – that is, RNA viruses that replicate by reverse transcriptase – was already well known and widely accepted. But, there was a widespread belief that activating – that means replicating retroviruses – did not exist in human beings, partially because there had been an extensive search for them that was entirely negative. Then there was a secondary belief that even if human retroviruses did exist, they were not really involved in the pathogenesis of major human diseases. While there were some exceptions – you mentioned HTLV-1 as a cause of certain subacute T cell leukemias or, in some cases, tropical spastic paraparesis – many people felt that they, at most, played a minor role in the general public health. And then, when it was discovered and formally proven, by Gallo and Montagnier, that retroviruses really were the principle causative agent for AIDS, there was a sense of futility because it was felt that retroviruses, by their very nature, were inherently untreatable (Figure 1). This is for two reasons: They had a capacity to integrate into DNA of the host, and they could rapidly mutate due to the error-prone reverse transcriptase that they possessed, and both of those factors were felt to be essentially impossible barriers to the development of effective antiretroviral therapy. So, I think that was the feeling, that was the prevailing mood that we faced in 1984 when we began thinking very seriously about trying to develop antiretroviral agents, of which the first that went through our pipeline into human beings was AZT. That was done in a collaboration of what was then called the Burroughs-Wellcome Company and also academic investigators at Duke University.

AV: *The time in between when HIV was identified as the causative agent of AIDS and the identification of the nucleotide analogs as potentially useful antiviral drugs, and then finally the human trials and approval of AZT and getting AZT into the clinic took only about two years...*

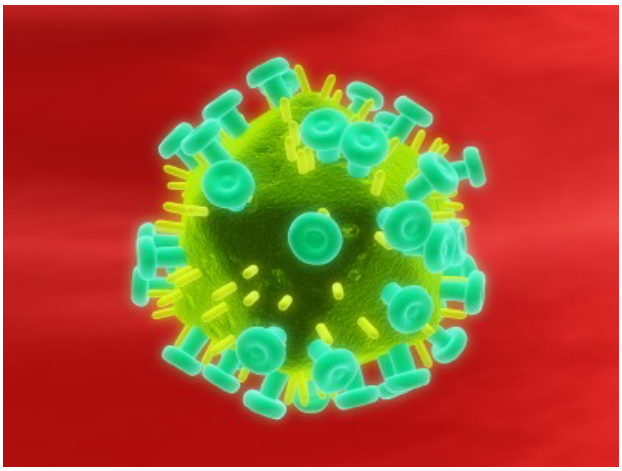

Figure 1: Human immunodeficiency virus (HIV) is a member of the retrovirus family that causes acquired immunodeficiency syndrome (AIDS). [Credit: ©iStockphoto.com/Sebastian Kaulitzki]

SB: It probably ranks among the most rapid timelines in modern pharmaceutical history. And I think it was a number of factors that made that possible. But, it is something that we were very fortunate to achieve.

AV: *What was there about the emergence of HIV and AIDS that enabled that – that made that happen so quickly?*

SB: AIDS, at the time, initially was an extremely mysterious disease, and it had appalling consequences. And it was associated with an enormous deterioration of the immune response, the onset of certain kinds of neoplasms, of which Kaposi's sarcoma is one, and it had a rapidly fatal outcome. It particularly also struck individuals in the prime of life, young individuals, and that, in turn, added an extra dimension of urgency. But, I think one of the things I want to just stress is the environment, or culture, in which a research program exists, is immensely important to this kind of discussion. I was very lucky to be part of the National Cancer Institute Intramural Program, and I think the location of my group within the Intramural Program of the National Cancer Institute had very special benefits for this antiretroviral drug discovery and development. And to add to that, the NCI, at the time, placed a very high priority on novel drug development and had considerable expertise in the clinical pharmacology and toxicology. And then the leadership at NCI at the time endorsed the philosophy that really is based on what Arthur C. Clarke has said, illustrating what it takes to break paradigms. And that is, the leadership at NCI endorsed the philosophy that, in order to discover the limits of what you think is possible, you sometimes have to go a little way past them into the territory of the impossible, and the boundaries

constantly shift, in any case. But, if you're totally afraid of crossing into the line of what might be impossible, if you're very fearful that that will make you somehow look bad or that you'll look foolish or something, you can't really make major advances, in my opinion. And the NCI really strongly supported translational medicine, although that term was not in use at the time.

AV: *In your Perspective, you mention the need to adopt new paradigms for funding and for expediting the process of developing treatments and getting them into patients. And specifically, you mentioned the need for collaboration between the public and the private sectors. Why is neither sector ideally suited to successfully manage these large studies on their own, and how would the collaboration of the two be able to improve translational efforts?*

SB: It isn't merely the large studies that we're talking about – that's part of the equation – but actually there's a larger issue. I think that certain types of drug discovery and certain types of drug development can be done in the private sector extremely well, but the private sector cannot undertake certain types of basic research or translational research when there is a significant chance of failure and when many of the assumptions are not proven. And so, it becomes very difficult to take on certain types of very far-reaching, paradigm-shifting experiments and to move them into the clinic and to move them to registration. That requires collaboration with the academic community and with the Intramural Program of the National Institutes of Health. So, a translational medicine approach, in which the probability of success or time to completion can't be precisely quantified, would be beyond the reach of many drug development programs – quite frankly, either private or publicly funded. The other thing that I want to stress is that we need to have a wholeness of motion between the lab and the clinic. I think a compartmentalization –in which people do discovery in the lab and then almost like a relay race, turn it over to people in the clinic who are possibly in a different administrative structure or geographic location – can work, but it does not really take the best advantage of what translational medicine means, in my opinion. So, we need to restore and replenish the notion of the wholeness of motion where clinical investigators can actually do basic research and vice versa. And I think that that is becoming more and more difficult. Think there is a specialization – it's an understandable specialization – but I think it would be important to have as many opportunities to fund, support, and train individuals who can do this wholeness of motion – that is, moving from the lab to the clinic and vice versa, from the clinic back to the lab.

Read the full transcript of the Podcast: http://stm.sciencemag.org/content/suppl/2010/07/05/2.39.39pc5.DC1/ScienceTranslMed_100707.pdf

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Erratum

The authorship was originally attributed to Samuel Broder (Celera, Alameda, CA, USA) and Annalisa VanHook (American Association for the Advancement of Science, Washington D.C., USA).

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