HOW MY 1983 IDEA FOR A SUPER-RESOLVING SINGLE-MOLECULE FLUORESCENCE MICROSCOPE INDEPENDENTLY WON THE 2014 NOBEL PRIZE IN CHEMISTRY

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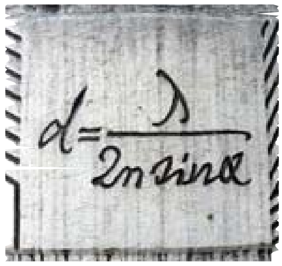
This paper documents how one of the author's inventions, sketched in 1983 in his notebook and published nowhere else, came to be independently developed and won Eric Betzig and others the 2014 Nobel Prize in Chemistry. The concept was to take multiple sequences of images of the same object, randomly lit by fluorescent light one molecule at a time, digitally process these images and combine them in a final image so sharp it goes beyond the theoretical resolution limits set by Abbe for microscopes. As confirmed by the company's present CEO the basic idea was mentiond in an awards application to Carl Zeiss company in1995. Now Zeiss is manufacturing microscopes based on the same principle, revolutionizing biological and medical research because it allows the imaging of live cells in unprecedented finely resolved detail.

From around 1980 I started an intensive program of self-study in optics[1] that lasted for decades, and my initial focus was super-resolution telescopes. I joined the Optical Society of America and SPIE the International Society for Optics and Photonics, invented and experimented on many schemes such as Calibrated Digital Imaging Systems, auto-stereoscopic displays, and made experiments applying my new theory of Streamline Diffraction to cancel diffraction effects (see the Physics section of my website for details) . Before the latter invention however, in 1983 I jotted down in my notebook an idea for a super-resolving microscope based on the concept of time resolved single views of individual self-luminous molecules.



I did not publish the idea anywhere, but in the summer of 1995 I mentioned it in my application (attached as an Appendix) for the 1996 Carl Zeiss Research Award offered by the famed optics company co-founded by Ernst Abbe. It was Abbe himself who in the 19th c. set the diffraction-limits to microscope resolution that my idea sought to surpass. Abbe's formula literally set in stone at Jena (photo on right) says that microscope resolution more than about half the wavelength of light is impossible. Imagine the mixture of surprise and pride when microscopes based on essentially an identical concept were announced in 2011 by Dr. Eric Betzig and his team.**See the announcement and my comments at physicsworld.com.** A greater surprise came in 2014 when Dr. Betzig and two others won the 2014 Nobel Prize in Chemistry for this work. Zeiss has developed sophisticated microscopes based on the same basic principle which they call photo activated localization microscopy **PALM.** Asked to comment on this coincidence, Zeiss convincingly denied my idea was passed on to the Nobel laureates.

In his **Nobel lecture** Dr. Betzig mentioned a long list of researchers including himself who worked hard to overcome technical difficulties related to getting molecules to shine individually, to achieve super-resolution beyond the theoretical Abbe limits.

Whoever had the idea first, it is humanity that is the ultimate winner because such microscopes can image living cells with great clarity, an invaluable new tool for medical research. **A recent article "Beyond the Limits" in Nature journal including my comment,** explains the technology and impact of the new florescence super-resolving microscopes, and how they are revolutionizing cell research in biology - hence in medicine.

Compare my 1983 notes below scanned from my notebook books of the time, with the slide and figure from the Nobel Prize announcement website in 2015.

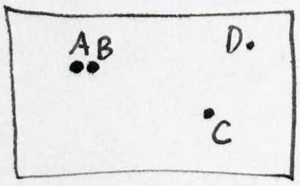
1 *Influences and Motivations in the Work of a Palestinian Artist/Inventor* .Leonardo 24 No.1, pp7-14, 1991© 1991 ISAST Pergamon Press
reprinted at **http://vladimirtamari.com/influences.html**

6 July 1983

MICROSCOPY: SUPERRESOLUTION THROUGH TIME-RESOLVED SCINTILLATION ILLUMINATION.

This proposal depends on finding a method of illuminating an object by point sources in contact with portions of the object randomly, & over a period of time having all points of object illuminated. Imaging is achieved by recording in time the various point images and adding them up. If the process is fast enough this can be accomplished nearly in real-time. Superresolution is assured because individual image points will emit separately & no interference with neighbouring points will occur at any one time.

Example: Let A & B be object points nearer to each other than can be normally resolved. With random scintillation illumination, at a time t_1 let points A & C be illuminated.



object space.

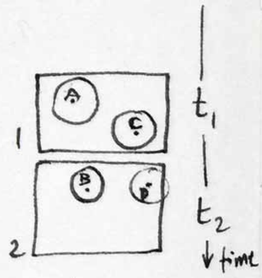
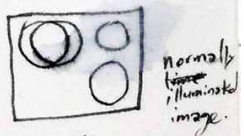
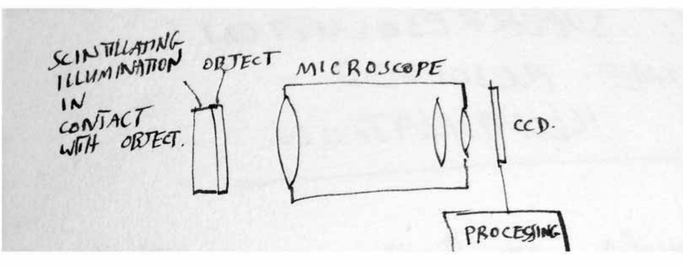


image space.

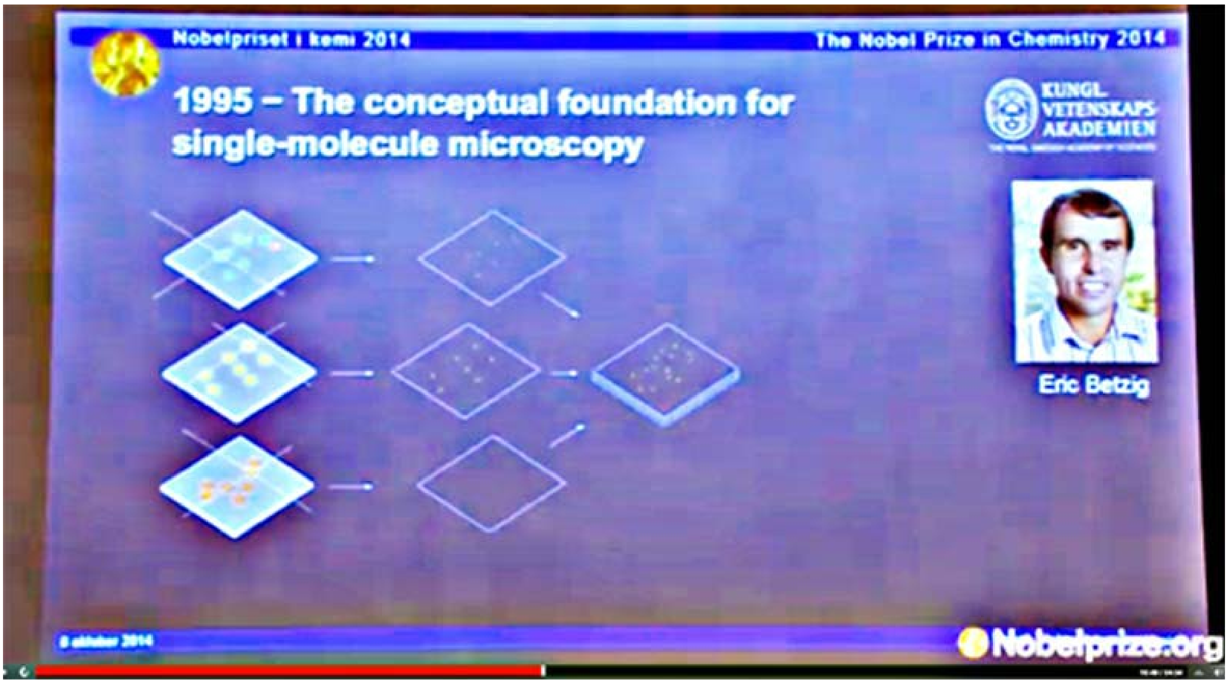


The image is recorded digitally. At another time t_2 points B & D might be illuminated & recorded — because the airy rings of A & B are seen at different times, they can easily be resolved & a processed image printed out.



DRAWING ON VERSO

My 1983 notes and sketches for taking sequential images normally blurred by diffraction (at times t1..t2..) of 'scintillating' i.e. fluorescent molecules and combining them into one highly detailed image. Because the molecules emit light randomly one at a time, their images in some sequences may not overlap and their position is known with high precision beyond the Abbe diffraction limits.



The slide shown when the Nobel Prize in 2014 was announced explaining how Dr. Betzig's microscope works.

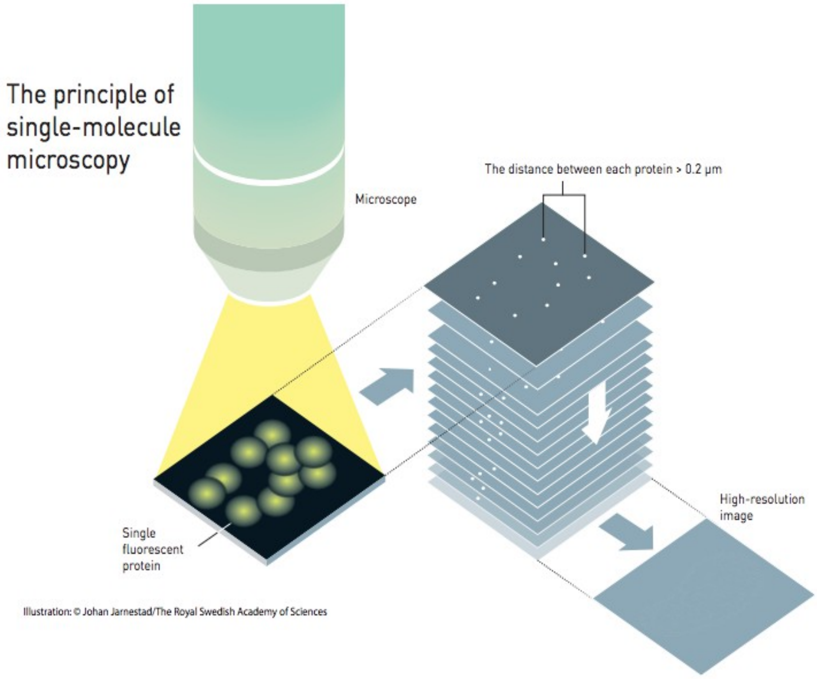


Figure 4 from The popular explanation on the Nobel Prize website of Dr. Betzig's method. Notice how the stack of images taken at different times are combined into a single image, exactly how I imagined and noted the process!

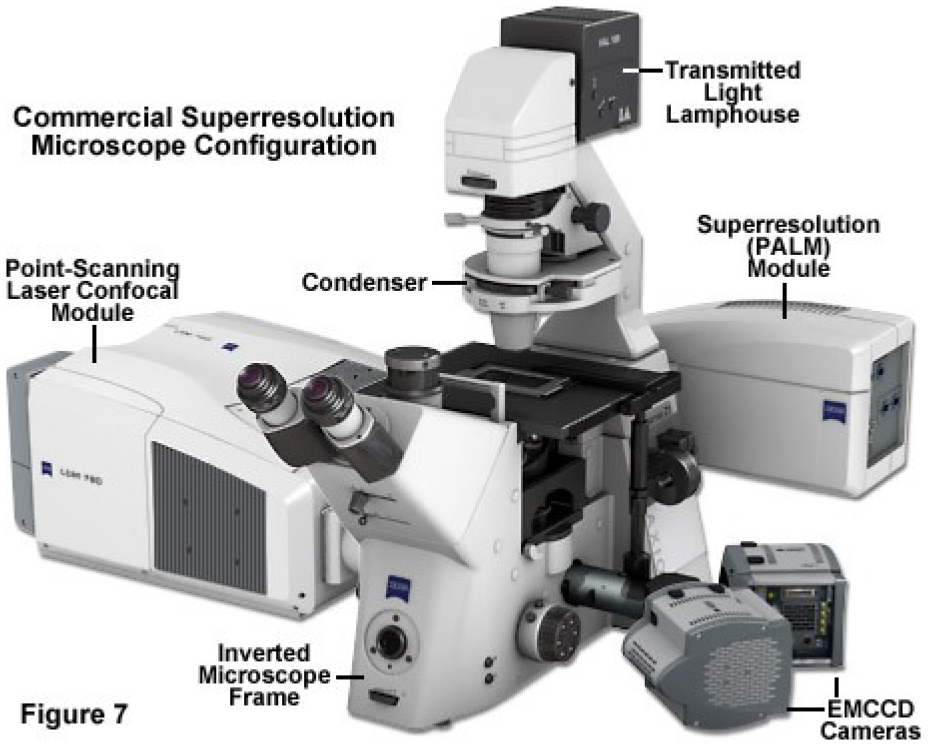


Figure 7

A Zeiss state-of-the-art microscope designed for superresolution imaging with PALM modules that operate with on same basic principle of time-resolved florescent imaging invented by the author.

Image Credit:R. Dyche Mullins/Lillian Fritz-Laylin/Megan Riel-Mehan.
A live cell imaged by the type of microscope described here.

Prof. Dr. Michael Kaschke

ZEISS

Carl Zeiss AG • Carl-Zeiss-Strasse 22 • 73447 Oberkochen • Germany

Tamari 3DD Co. Ltd
Mr. Vladimir Tamari
4-2-8-C26 Komazawa, Setagaya-ku
154-0012 Tokyo
Japan

19.11.2015

Your inquiry from October 2015

Dear Mr. Tamari,

Thank you for your inquiry and for approaching me directly.

Microscopy is a very exciting field of research and innovation. And although distinctly lasting for more than hundred years now there are still great breakthroughs which partially were awarded with Nobel Prizes.

Indeed you applied for the 1996 Carl Zeiss Research Award. And besides your description about your work on de-diffraction you listed the term "super-resolved" microscopy by time-resolved imaging of faint self-luminous objects" dated back to 1983 in your application.

At ZEISS we cultivate an open and fair cooperation with our external partners. Neither such applications are considered for generating ideas in general, nor single terms out of it are of use to do so. Moreover, please note that we definitely express complete confidence in our referee panel of the Carl Zeiss Research Award.

Furthermore, we appreciate your offer regarding super-resolution related topics. However, we do not consider them to be relevant to our current business in microscopy.

Sincerely,

Michael Kaschke

Carl Zeiss AG
Prof. Dr. Michael Kaschke
President & CEO

Carl-Zeiss-Strasse 22
73447 Oberkochen
Germany

Phone: +49 7364 20-8200
Fax: +49 7364 20-8220
Email: michael.kaschke@zeiss.com

Commercial register:
Ulm, HRB 501 555

Letter from the President and CEO of Zeiss kindly confirming the mention of my 1983 super-resolved microscope concept in 1996. Because I never developed or published my invention, this letter is the only public confirmation of my priority for the invention of this type of microscope.

APPENDIX

Copies of Vladimir F. Tamari's correspondence and application documents concerning the 1996 Carl Zeiss Awards (sent in the summer of 1995). The sentence describing the 1983 superesolution microscopy idea is highlighted in yellow.

Carl Zeiss Research Award

1996

Every two years the Ernst Abbe Fund presents the Carl Zeiss Research Award. It is conferred for outstanding scientific achievements in basic research and applications in the overall field of optics. The sum allocated to the award totals

DM 50,000.–

The award is aimed primarily at qualified, preferably young scientists. The achievements of individuals or of small groups will both be taken into consideration.
Recommendations and personal applications should be sent before

September 30, 1995

to
Ernst-Abbe-Fonds im
Stifterverband für die Deutsche Wissenschaft
Barkhovenallee 1
Postfach 16 44 60

D-45224 Essen

enclosing a review of the scientific work on which the application is based, a curriculum vitae and a brief outline of the candidate´s scientific career.

The award will be presented during the annual meeting of the German Society for Applied Optics (DGaO) on May 31, 1996 in Neuchâtel/Switzerland.

ERNST ABBE FUND

Member of the Donors´Association
for the Promotion of Science
and the Humanities in Germany

Circle No. 436

The announcement of the Award published in a magazine specialized in optical research

VLADIMIR F. TAMARI

Curriculum Vitae

1942	Born in Arab Jerusalem, Palestine
1949-57	Friends Boys School, Ramallah
1967-61, 63	Studied physics and then art , American University of Beirut, Lebanon
1961-62	Studeied painting at St. Martin's School of Art, London
1962-64	Invented improved Arabic type design, invented 3D drawing instrument Corresponded with NASA about an idea for lunar mapping
1965-66	Pendle Hill School, Pennsylvania, U.S.A.
1966-70	Employed as film technician and illustrator, UNRWA-UNESCO Beirut.
1970-95	Self-employed in Japan as artist, inventor and researcher in physics. Also taught at Tokyo University, worked for Radio Japan, illustrated children's books, and held exhibitions of 3D drawings and watercolor paintings throughout Japan, also in the Middle East, Europe (including Germany, Austria and Switzerland) and the U.S.

- At various times member of Optical Society of America
  SPIE - International Society for Optical Engineering
  Japan Graphic Science Society
  Union of Palestinian Artists

- Held post as International Co-Editor, *LEONARDO* Journal (Pergamon Press, Oxford)

- Citizen of Jordan. Married to Kyoko Miyakoshi since 1967, with two daughters Mariam and Mona. Orthodox Christian faith.

- Reference: Dr. Hanna M. Nasir, President, Bir Zeit University, Bir Zeit, West Bank.

REVIEW OF MY DE-DIFFRACTION RESEARCH

DE-DEFFRACTION , (DD), is the method I invented for creating diffraction-free waves in any kind of field, including electromagnetic, acoustic and fluid fields. DD allows superresolution beyond the "diffraction limits" in imaging and the propagation of beams such as lasers, without spreading. This will have revolutionary applications in such instruments as cameras, telescopes and radar, and in such devices as microwave antennas, optical memory storage and many others.

Mathematically, a DD field is a soliton, a wave that does not change its shape while propagating: solitons are known to exist in water waves and in subatomic particle fields, so theoretically it is possible to have soliton solutions for other waves, for example in non-diffracting microwave beams that can go to the moon without spreading, or an imaging radar field superfocussed to a point much more intense and concentrated than the 'diffraction-limited' Airy function.

Starting from 1980 I started an intense course of self-study and experimentation in modern optics, carried on at home to try to improve telescope resolution. I developed analog-digital calibration methods and others where annular aperture configurations are linked to algorithms used to digitally restore an image and achieve super-resolution beyond the Raylegh limits. This was my goal.

In late 1984 I had an idea that if diffraction was the fan-like spreading of the energy streamlines of the field as they leave the aperture, then it can be cancelled by simply refocusing these streamlines mostly within a wavelength near the aperture edge. I experimented with water and ultrasound waves generated by reflectors with curved edges, and observed qualitatively that diffraction is cancelled or reduced. I am now very confident that DD works perfectly, and that its study has to be carried on by those more qualified than me both in theoretical analysis and practical applications.

There were three sources of difficulty in carrying out my DD research. One was the fact that I was an amateur working practically alone with minimum equipment. The other was the stress and worry that DD will have important military applications, and so I tried to send my results both East and West. The third difficulty was theoretical: From the start, Heisenburg demonstrated his uncertainty principle by showing how a photon diffracts and its position is therefore uncertain. But a non-diffracting laser beam will have its position and momentum vectors fully determined at all times. How can quantum considerations allow DD? Over the years I have tried to cope with this difficulty and I have outlined a theory whereby these contradictions are reconciled. But I think it is only fair to await experimental verification of DD before tackling these theoretical considerations.

It is possible to test DD by the methods I referred to in my patents and papers enclosed here, for example giving an aberration-free lens a bevel edge a few hundred wavelengths wide. (Note: the curves described on p.75 of my *Optoelectronics* paper are correct only qualitatively. And testing DD by computer simulations based on the Huygens principle simply will not work, because it is an approximation that fails to describe the field within a wavelength of the aperture edge).

OUTLINE OF MY INVENTIONS AND SCIENTIFIC RESEARCH

As an independant self-employed researcher, I have made scores of inventions in different fields. Knowledge of one field often inspired work in another. Some of the following ideas have been developed into commercial products, while others remain in my notebooks. In some cases I have written and sometimes published papers about these ideas (see following page). For economic reasons I have applied for patents for only a few of my inventions.

IMAGING / OPTICAL INVENTIONS:

- **Calibration of scanning-radar response *in situ*, electronically subtracted from new scans of the same location, to show objects in the presence of noise (1968)**
- **Stereoscopic camera focusing method (1975)**
- **Analog-Digital calibrating method for any imaging instrument in general, allowing imaging with highly distorted optics (1980)**
- **Annular aperture design ombined with image processing to obtain superresolution (1982)**
- **Scanning with a point source to generate autostereoscopic images (1981-83)**
- **Superrsolved microscopy by time-resolved imaging of faint self-luminous objects (1983)**
- **The Cancellationof Diffraction (1984-95) *(papers and patents listed next page)***
- **Combining Lippmann's autostereoscopic and color photography concepts in a new incoherent holographic system (1995)**

DRAWING INSTRUMENTS:

- **Stereoscopic 3D Drawing Instruments (1964-80)**
  Stereoscopic Drawing Instrument: (Japanese Patent No. 762196 -1975)
- **Instrument to Draw Sun's Shadow for Architects (1979)**
  (Japanese Patent Applic. No. 55-160799-1980)
- **Perspective Drawing Device (1980)**
  Mechanical Perspective Drafting Device (U.S. Patent No. 4,672,749 -1987 and Japanese Patent No.59-131519- 1992)
- **A spiral compass (1981)**

MANY OTHER INVENTIONS INCLUDING:

- **Arabic Typography System (1962)**
  Improvements in Printing (British Patent No, 1011006- 1963)
- **Underwater and Dam Construction Using Freezing Methods (1963)**
- **New Concepts in Retractable Dome Design (1988)**
- **New Concepts in Wheel Design (1990)**

OPTICS PAPERS BY VLADIMIR TAMARI.

"Calibrated Digital Imaging Instruments": A system whereby the instrument's point response function is physically calibrated simultaneously in the object and the image fields pixel by pixel. The resulting matrix is used to efficiently restore even highly distorted images.*(With Capt.M. Kobori.1982, unpublished).*

"From 3D Drawings to 3D Focusing": A review of V. Tamari's work in stereoscopic drawing, with a proposal that camera focusing mechanisms be linked to a luminous sign suspended in visual space through binocular viewfinders. (Camera Review, Tokyo, Stereoscopy Issue, August 1984)

"The Cancellation of Diffraction In Wave Fields": An analytic and general survey of methods to obtain superresolution, and my ideas for the cancellation of diffraction. (Optoelectronics **2** No. 1, 59-82 Tokyo ,Mita Press, June 1987)

"From Diffraction to De-diffraction": A rigorous mathematical demonstration of the concepts of de-diffraction. (1993, *unpublished*)

"United Dipole Field": Shows that any dipole field (for example a charged particle near its anti-particle) consists of a pattern of curved streamlines, which can be interpreted in equivalent electromagnetic, gravitational and quantum-mechanical ways (1993, *unpublished*).

"Method and Means to Cancel Diffraction Effects from Radiation Fields": Contains a lengthy analysis of the proposal that a de-diffracted wavefront has curved edges (U.S. Pat. 5,148,315 - 1992)

"De-diffraction Methods"; A short improvement over the basic DD patent, describing how a wavefront (with small wavelength compared to the aperture) having simple bevel edges can minimize diffraction.(U.S. Pat. 5,392,155 - 1995)

"Influences and Motivations in the Work of a Palestinian Artist/ Inventor": contains an autobiographical explanation of how the De-Diffraction idea came about.
(Leonardo **2**, No.1 Pergamon Press,
Oxford,1991)

ERNST-ABBE-FONDS

IM STIFTERVERBAND

FÜR DIE DEUTSCHE WISSE

Vladimir F. Tamari
President
Tamari 3DD Co. Ltd.
4-2-8-C 26, Komazawa
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JAPAN

Carl-Zeiss-Forschungspreis und
Otto-Schott-Forschungspreis

09.10.1995/ku

Carl Zeiss Research Award 1996

Dear Sir,

many thanks for your application for the Carl Zeiss Research Award 1996.

The received documents will be sent to the Endowment Committee.

As soon as possible we will inform you about the Committee's decision.

Sincerely yours,

ERNST-ABBE-FONDS im
Stifterverband für die Deutsche Wissenschaft

(Klaus Kuli)

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45239 Essen (Heidhausen) | Telefax (02
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JAPAN

Carl-Zeiss-Forschungspreis und
Otto-Schott-Forschungspreis

25.01.1996

CARL ZEISS RESEARCH AWARD 1996

Dear Sir,

thank you for your application for the above mentioned award.

The Committee of the ERNST-ABBE-FONDS had to make a selection from a great number of excellent applications and proposals.

After careful consideration the Committee nominated

Dr. Dieter W. Pohl, IBM Zürich/Research Laboratory and

Dr. Eric A. Cornell, University of Colorado/Boulder

as winners of the award 1996.

We wish you all the best for your further work.

Yours sincerely,
ERNST-ABBE-FONDS im
Stifterverband für die Deutsche Wissenschaft

(Dr. Ambros Schindler)

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