UNIVERSITATEA DE VEST DIN TIMIȘOARA

Doctor Honoris Causa
SCIENTIARUM

Prof. dr. Dr. h. c. mult.
STEFAN W. HELL
Laureat al Premiului Nobel pentru Chimie

Timișoara, 31 mai 2019

Cuvânt
la deschiderea ceremoniei de acordare a titlului de
DOCTOR HONORIS CAUSA SCIENTIARUM
al Universității de Vest din Timișoara
domnului prof. dr. Dr. h. c. mult. Stefan Walter HELL

Stimate domnule profesor Ștefan W. Hell,
Stimați membri ai comunității academice,
Stimați invitați,
Dragi studenți,
Onorat auditoriu,

Comunitatea Academică a Universităţii de Vest din Timişoara este preocupată constant atât de promovarea celor mai remarcabile rezultate ştiinţifice, cât şi de elogierea şi recunoaşterea meritelor marilor personalităţi ale lumii ştiinţifice mondiale care au lăsat o amprentă importantă asupra cunoaşterii umane. Nu poate fi nimic mai onorant pentru o universitate decât să primească în rândurile doctorilor săi onorifici o personalitate ca cea a domnului Profesor Stefan Hell, laureat al Premiului Nobel pentru Chimie. Semnificaţia acestui moment este de o însemnătate aparte, domnul Profesor Hell fiind născut în partea de Vest a României, model de multiculturalitate, locul de unde a pornit revoluţia română din 1989 şi locul care va fi Capitala Culturală a Europei în 2021.

Profesorul Stefan Hell provine dintr-o familie de șvabi bănățeni. A copilărit la Sântana, în județul Arad, unde a urmat școala elementară. În anul 1977 a fost admis la Liceul Nikolaus Lenau din Timișoara, ale cărui cursuri le-a urmat până în 1978, când a emigrat cu familia în Republica Federală Germania.

A studiat fizica la Universitatea din Heidelberg (1981-1987). A obţinut titlul de doctor în fizică la aceeaşi universitate în anul 1990, cu lucrarea „Reprezentarea microstructurilor transparente în microscopul confocal”. Întreaga carieră ştiinţifică şi-a consacrat-o îmbunătăţirii rezoluției microscopiei optice dincolo de limitele atinse până la acel moment de știință, astfel punând bazele microscopiei 4Pi, o variantă îmbunătățită a microscopiei de fluorescență.

În prezent, Stefan W. Hell este director al Institutului Max Planck pentru Chimie Biofizică din Göttingen, director al Institutului Max Planck pentru Cercetări Medicale din Heidelberg şi director al unui Departament al Centrului German de Cercetare a Cancerului din Heidelberg. Este profesor onorific de fizică experimentală la Universitatea din Göttingen și profesor de fizică la Universitatea din Heidelberg. Este membru al Academiei de Științe din Göttingen și Heidelberg, precum şi membru de onoare al Academiei Române din anul 2012.

Ștefan W. Hell are meritul de a fi conceput, validat și aplicat prima idee viabilă de depășire a barierei Abbe de rezoluție la un microscop optic. Rezoluția spațială obţinută a condus la înregistrarea cu succes a dinamicii mitocondriale în celule de drojdie cu un microscop 4Pi.

A publicat peste 400 de lucrări ştiinţifice (dintre care 48 în prestigioasele reviste Nature și Science) și a primit mai multe premii, printre care Premiul Comisiei Internaționale de Optică (2000), Premiul de cercetare Carl Zeiss (2002), Premiul de inovare al președintelui Germaniei (2006), Premiul Julius Springer pentru Fizică Aplicată (2007), Premiul Leibniz (2008), Premiul de Stat al Saxoniei Inferioare (2008), Premiul Otto-Hahn pentru Fizică (2009), Premiul Kavli pentru nanoștiinţe (2014) şi premiul Nobel pentru chimie în 2014.

Stimate domnule profesor dr. Dr. h. c. mult. Stefan Hell,

Prin acordarea titlului de **Doctor Honoris Causa Scientiarum**, Universitatea de Vest din Timişoara recunoaşte meritele dumneavoastră deosebite pe tărâmul ştiinţei şi este convinsă că, prin alăturarea Domniei Voastre comunităţii academice pe care o reprezint, prestigiul intituţiei, din care acum faceţi parte, se va consolida. Suntem convinşi că prezenţa dumneavoastră în rândul doctorilor onorifici ai Universității de Vest din Timișoara va fi un puternic catalizator pentru studenţii care au ales să înveţe limbajul ştiinţei.

Vă urez multă sănătate şi putere de muncă, pentru a putea sluji cu aceeaşi pasiune şi dăruire progresul cunoaşterii umane.

Prof. univ. dr. Marilen-Gabriel Pirtea

Rectorul Universității de Vest din Timișoara

Address

at the opening of the ceremony for awarding the title of

DOCTOR HONORIS CAUSA SCIENTIARUM

of the West University of Timișoara

to prof. dr. Dr. h. c. mult. Stefan Walter HELL

Dear Professor Stefan W. Hell,
Distinguished members of the academic community,
Dear guests,
Dear students,
Ladies and Gentlemen,

The academic community of the West University of Timișoara is constantly concerned with promoting the most remarkable scientific results, as well as with praising and acknowledging the merits of the world's greatest scientific personalities, who left their important imprint on human knowledge. Nothing can be more flattering for a university than to receive among its honorary doctors a personality like that of Professor Stefan Hell, winner of the Nobel Prize for Chemistry. The significance of this moment is all the more special, since Professor Hell was born in the western part of Romania, a multicultural model, the place where the 1989 Romanian Revolution began and the city that will be European Capital of Culture in 2021.

Professor Stefan Hell belongs to a family of Banat Swabians. He spent his childhood in Sântana, Arad county, where he studied at the elementary school. In 1977 he was admitted at Nikolaus Lenau Highschool in Timișoara, where he studied until 1978, when, together with his family, he emigrated to the Federal Republic of Germany.

He studied physics at the University of Heidelberg (1981-1987). He obtained his PhD in physics at the same university in 1990, with the thesis „The Representation of Transparent Microstructures in the Confocal Microscope". He devoted his entire scientific career to improving the resolution of optical microscopy beyond the limits established by science until that moment, thus laying the foundations for 4Pi microscopy, an improved version of fluorescence microscopy.

Currently, Stefan W. Hell is the Director of the Max Planck Institute for Biophysical Chemistry in Göttingen, Director of the Max Planck Institute for Medical Research in Heidelberg and Director of a Department within the German Centre for Cancer Research in Heidelberg. He is an honorary professor of experimental physics at the University of Göttingen and professor of physics at the University of Heidelberg. He is a member of the Science Academy of Göttingen and Heidelberg, as well as honorary member of the Romanian Academy since 2012.

Stefan W. Hell has the merit to have conceived, validated and applied the first viable idea to go beyond the Abbe resolution limit in an optical microscope. The spatial resolution obtained led to the successful recording of mitochondrial dynamics in yeast cells with a 4Pi microscope.

He published over 400 scientific papers (of which 48 in prestigious journals such as Nature and Science) and received several awards, such as The International Optical Commision Award (2000), The Carl Zeiss Research Award (2002), The Innovation Award of the President of Germany (2006), The Julius Springer Award for Applied Physics (2007), The Leibniz Award (2008), The State Award of Lower Saxony (2008), The Otto-Hahn Award for Physics (2009), The Kavli Award for Nanosciences (2014) and the Nobel Prize for Chemistry in 2014.

Dear professor dr. Dr. h. c. mult. Stefan Hell,

By awarding you the title of **Doctor Honoris Causa Scientiarum**, the West University of Timișoara ackowledges your outstanding merits in science and I am sure that, after you join the academic community I represent, the prestige of the institution, whose member you are now, will increase. I am also convinced that your presence among the honorary doctors of the West University of Timișoara will be a powerful catalyst for the students who choose to learn the language of science.

I wish you good health and strength to continue the progress of human knowledge with equal passion and dedication.

Prof. Marilen-Gabriel Pirtea, PhD.

Rector of the West University of Timișoara

LAUDATIO
în onoarea
domnului prof. dr. Dr. h. c. mult. Stefan Walter HELL
cu ocazia acordării titlului de
DOCTOR HONORIS CAUSA SCIENTIARUM

Stimate domnule Rector,
Stimate domnule Preşedinte al Senatului UVT,
Stimaţi membri ai Comunităţii Academice,
Distinsă asistenţă,

Comunitatea academică a Universităţii de Vest din Timişoara are deosebita bucurie de a participa la decernarea titlul onorific de Doctor Honoris Causa Scientiarum domnului prof. dr. STEFAN W. HELL, una din cele mai mari personalităţi ale prezentului în domeniul microscopiei de înaltă rezoluţie, **laureat al Premiului Nobel pentru chimie în 2014** alături de Eric Betzig şi William E. Moerner pentru „**dezvoltarea microscopiei cu fluorescenţă de super-rezoluţie**", potrivit comitetului Nobel.

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Domnul prof. dr. STEFAN W. HELL s-a născut la Arad la 23 decembrie 1962, având părinţii din Comuna Sântana – localitate fondată de emigranţii germani (şvabi) în secolul 18. Limba maternă a fost un dialect al limbii germane – vorbit în sud-vestul Germaniei. Tatăl său a fost inginer, iar mama dascăl la şcoala primară. A urmat studiile primare şi gimnaziale în limba germană la Şcoala din Sântana. Din acei ani, Profesorul Ştefan W. Hell evocă în biografia sa imaginea tinerilor săi profesori de la şcoala din Săntana, şi în special a Domnului Hans Kling (profesorul de chimie), foarte convingător în explicarea structurii atomice şi uimirea încercată în acei ani de faptul că cea mai mare parte a masei atomice se regăseşte în nucleu.

După cele opt clase la Şcoala din Sântana, tânărul Ştefan W. Hell ajunge la Liceul Nikolaus Lenau din Timișoara, unul dintre cele mai bune licee din țară, la o clasă de matematică-fizică. Aici a ajuns să îndrăgească fizica şi chiar a şi câştigat un concurs local de fizică.

Dar tot în acei ani, a conştientizat că România era departe de ceea ce-şi putea dori un tânăr, iar regimul Ceauşescu a făcut ca majoritatea etnicilor germani din Banat să-şi dorească emigrarea. Emigrarea unuia din colegi, diagnosticul mamei şi sfatul unui medic l-au făcut pe tânărul Ştefan Hell să-şi convingă părinţii să aplice pentru o viză de emigrare. După doi ani de incertitudini şi neplăceri familia Hell a fost lăsată să plece cu câteva obiecte personale în 8 aprilie 1978. Familia Hell, având rude în Germania de Vest s-a stabilit în Ludwigshafen, un oraş industrial la vest de râul Rin, departe de cortina de fier, dar la doar câţiva kilometri de Universitatea din Heidelberg.

Greutăţile inerente începutului noii vieţi în Ludwigshafen prin care a trecut familia Hell, în ochii tânărului Stefan au fost compensate de noile oportunităţi ale Occidentului. La şcoala

secundară din Ludwigshafen a constatat că era cu mult înaintea colegilor în ceea ce privește științele, dar problema era cu limba engleză, deprinsă doar din filmele vizionate în România. Încurajat de profesorul de fizică (dl Ecker), viitorul laureat Nobel reușește să absolve doar cu limba franceză – ca limbă străină (studiată şi în România) - chiar cu un an mai devreme.

În 1981 Stefan W. Hell începe studiul fizicii la Universitatea din Heidelberg, surprins totuşi de faptul că materialul de studiu nu era alterat de chestiuni politice.

Parcursul profesional:

- 1981-1987 studiază fizica la Universitatea Heidelberg
- 1990 obţine titlul de doctor în fizică la Universitatea Heidelberg cu lucrarea „Reprezentarea microstructurilor transparente în microscopul confocal" sub îndrumarea profesorului Siegfried Hunklinger
- 1991 – 1993 Cercetător postdoctoral la EMBL (European Molecular Biology Laboratory)
- 1993 – 1996 Principal Investigator, Grupul de Microscopie Laser; Univ. Turku, Finlanda
- 1996 Doctor Habil. în Fizică, Univ. Heidelberg; Profesor de fizica din 02/1996
- 1997 – 2002 Conducătorul Junior Group Max-Planck de Microscopie optică de înaltă rezoluţie, la Institutul Max-Planck Chimie Biofizică Göttingen, Germania
- din 10/2002 Director la Institutul Max-Planck Chimie Biofizică, Şeful Departmentului de NanoBiofotonică
- din 12/2003 Apl. Prof., Facultatea de Fizică, Univ. Heidelberg
- din 12/2003 Şeful Diviziei de Microscopie optică de înaltă rezoluţie, DKFZ Heidelberg
- din 01/2004 Prof. onorific, Facultatea de Fizică, Univ. Göttingen
- 2014 Premiul Nobel în Chemie

Opera ştiinţifică a prof. dr. STEFAN W. HELL impresionează prin cele peste 400 publicaţii ştiinţifice, peste 25000 de citări şi un indice Hirsh 91 pe WEB of Science şi peste 27000 de citări şi un indice Hirsh 85 pe Scopus. Publicaţiile sale sunt, în marea lor majoritate, publicate în reviste de mare prestigiu (foarte multe în SCIENCE, NATURE, NATURE COMMUNICATIONS, PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, NATURE METHODS, NANO LETTERS, OPTICS LETTERS, BIOPHYSICAL JOURNAL, OPTICS EXPRESS, JOURNAL OF MICROSCOPY OXFORD etc.) și recunoscute ca atare de comunitatea științifică.

Lucrările prof. dr. Dr. h. c. STEFAN W. HELL tratează probleme de pionierat în domeniul microscopiei optice de superrezoluţie, cu largi aplicaţii în nanoştiinţe şi nanotehnologii.

Domeniul predilect de cercetare în care prof. dr. STEFAN W. HELL s-a exprimat la cel mai înalt nivel ştiinţific în care şi-a dovedit şi validat excepţionalul potenţial creativ, au fost: contribuţia de pionierat la spargerea limitei de rezoluţie a microscoapelor optice – limitată la jumătate din lungimea de undă a luminii incidente – limită stabilită din 1873 de Abbe. Microscopul 4Pi reprezintă prima mare realizare a lui Stefan Hell, dat fiind că acesta a condus la obţinerea unei rezoluţii de ordinul a 100 nm, care corespunde unui spot focal sferic de câteva ori mai mic decât cel obţinut în microscopia confocală.

În 1999-2000, a urmat o nouă descoperire importantă: microscopia cu baleiaj laser bazată pe golire prin emisie stimulată (STED-stimulated emmision depletion). Principiul pe care l-a utilizat este foarte simplu. În loc să ai un microscop cu o singură sursă de lumină, respectiv în cazul nostru să înlocuieşti lumina albă cu laser, el ilumina proba cu un alt fascicul laser care producea o tranziţie între două nivele atomice. Emisia care era produsă de această excitare cu un alt laser făcea ca dimensiunea spotului cu care se observa proba să devină de o mie de ori mai mică decât aceea a laserului cu care se făcea observarea, încât dintr-un spot foarte mare cu care se ilumina proba, cel care excita prelua ceva care era de o mie de ori mai mic. O idee extrem de simplă în sine, care este folosită şi în emisia laser.

Contribuţiile esenţiale mai sus menţionate l-au consacrat pe prof. dr. STEFAN W. HELL drept unul din pionierii şi liderii mondiali din domeniul nanoscopiei optice, fapt confirmat şi de acordarea a numeroase premii şi distincţii, culminând în 2014 cu acordarea premiului Nobel pentru chimie alături de Eric Betzig şi William E. Moerner pentru „**dezvoltarea microscopiei cu fluorescenţă de super-rezoluţie**”. Stefan Hell a fost distins cu premiul Nobel pentru introducerea, în anul 2000, a conceptului de "golire prin emisie stimulată" (STED/stimulated emission depletion) în microscopie.

Argumentul principal pentru care comisia de analiză propune şi susţine acordarea titlului de DHC al UVT este aplicabilitatea deosebită a dispozitivelor descoperite de prof. dr. STEFAN W. HELL în domenii precum biologia, medicina, ştiința materialelor, biochimie, biofizică, optică, fizică, nanoştiinţe şi nanotehnologii. Despre partea aplicativă a acestor descoperiri, Preşedintele Academiei Române, Academicianul Ionel Valentin Vlad spunea:

„Microscopul pe care l-a făcut Stefan Hell cu această descoperire extraordinară permite să se vizualize viaţa la nivel molecular, modul cum se comportă celulele, moleculele propriu zis în celulele vii”.

LAUDATIO
In honour of
Prof. Dr. Dr. h. c. mult. Stefan Walter HELL
Upon awarding the title of
DOCTOR HONORIS CAUSA SCIENTIARUM

Honourable Rector,
Mr. President of the WUT Senate,
Members of the Academic Community,
Distinguished guests,

The academic community of the West University of Timişoara is pleased and honoured to take part in the ceremony of awarding the honorary title of Doctor Honoris Causa Scientiarum to Prof. Dr. STEFAN W. HELL, one of the greatest personalities of this age in the field of super-resolution microscopy, a **laureate of the Nobel Prize for Chemistry in 2014,** together with Eric Betzig and William E. Moerner for "**the development of super-resolution fluorescence microscopy**", according to the Nobel committee.

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Prof. Dr. STEFAN W. HELL was born in Arad on December 23, 1962, his parents being originally from the village of Sântana – a settlement founded by German (Swabian) immigrants in the 18th century. His mother tongue was a dialect of German – spoken in the South-west of Germany. His father was an engineer, while his mother was a primary school teacher. His education began in the German-medium primary and secondary school of Sântana. Professor Stefan W. Hell recalls, in his biography, the image of his young teachers at the local school, especially Mr. Hans Kling (his chemistry teacher), who was very convincing in explaining the structure of the atom. He also remembers his surprise at learning that the greatest part of the atomic mass is found in the nucleus.

After the first eight grades at the Sântana School, the young Stefan W. Hell was admitted at the Nikolaus Lenau Highschool in Timișoara, one of the best schools in the country, in a class of Mathematics-Physics. Here, he grew fond of physics and even won a local contest in physics.

But, during this period, he also became aware that Romania was far from what a young man wanted, and the Ceauşescu regime made sure the majority of the German community wanted to emigrate. One of his classmates' emigration, his mother's disease and the doctor's advice determined the young Stefan Hell to persuade his parents to apply for an emigration visa. After two years of uncertainties and misfortunes, the Hells were allowed to leave the country with only a few personal belongings, on April 8, 1978. The Hells, with relatives in Western Germany, settled in Ludwigshafen, an industrial town at the west of the Rhine, far from the Iron Curtain, only a few miles away from the University of Heidelberg.

The hardships that naturally came with the new life in Ludwigshafen, experienced by the Hell family, in young Stefan's eyes, were compensated by the new opportunities offered by the West. While studying at the secondary school of Ludwigshafen, he realized he was much ahead of his classmates in sciences, but he had a problem with English, which he only knew from the films he had watched in Romania. Encouraged by his physics teacher (Mr. Ecker), the future Nobel laureate graduated only with French as a foreign language (which he had studied at school in Romania), a year ahead of his classmates.

In 1981, Stefan W. Hell started studying physics at the University of Heidelberg, still puzzling over the fact that the curricula was not altered by political issues.

Career:

- 1981-1987: he studies physics at the University of Heidelberg;
- 1990: he is awarded the PhD in physics at the University of Heidelberg with the thesis „Representing Transparent Microstructures in the Confocal Microscope" under the supervision of Professor Siegfried Hunklinger;
- 1991 – 1993: Postdoctoral researcher at EMBL (European Molecular Biology Laboratory);
- 1993 – 1996: Main investigator, the Laser Microscopy Group; Univ. Turku, Finland;
- 1996: Doctor Habil. in Physics, Univ. Heidelberg; Physics professor since 02/1996;
- 1997 – 2002: Leader of Max-Planck Super Resolution Optical Microscopy Junior Group, at the Max-Planck Chemistry Biophysics Institute, Göttingen, Germany;
- since 10/2002: Director of the Max-Planck Chemistry Biophysics Institute, Head of the Nano-biophotonic Department;
- since 12/2003: Apl. Prof., The Faculty of Physics, Univ. Heidelberg;
- since 12/2003: Head of the Super Resolution Optical Microscopy Division, DKFZ Heidelberg;
- since 01/2004: Honorary professor, the Faculty of Physics, Univ. Göttingen;
- 2014: the Nobel Prize for Chemistry.

The scientific work of Prof. Dr. STEFAN W. HELL is impressive, with more than 400 publications, over 25.000 citations and a Hirsh Index of 91 on the WEB of Science and over 27.000 citations and a Hirsh Index of 85 on Scopus. His studies are published, in their vast majority, in highly prestigious journals (many in SCIENCE, NATURE, NATURE COMMUNICATIONS, PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, NATURE METHODS, NANO LETTERS, OPTICS LETTERS, BIOPHYSICAL JOURNAL, OPTICS EXPRESS, JOURNAL OF MICROSCOPY OXFORD, etc.) and are acknowledged as such by the scientific community.

Prof. Dr. Dr. hc. STEFAN W. HELL's work tackles pioneering issues in super resolution optical microscopy, with vast application in nanosciences and nanotechnologies.

The main areas of research in which Prof. Dr. STEFAN W. HELL expressed himself at the highest level and in which he validated his exceptional creative potential were: his pioneering contribution to breaking the resolution limit of optical microscopes – limited to half the wave length of incident light – established by Abbe in 1873. The 4Pi microscope is Stefan Hell's first

great achievement, as it led to a 100 nm resolution, which corresponds to a spheric focal spot, several times smaller than the spot obtained in the confocal microscopy.

In 1999-2000, another important discovery was made: the swept field laser microscopy based on STED – stimulated emmision depletion. The principle he used was straight-forward. Instead of having a microscope with a single light source, in our case, replacing the white light with the laser, he lit the sample with another laser beam, which produced a transition between two atomic levels. The emission produced by this excitation with another laser made the size of the spot used to observe the sample to decrease one thousand times in comparison with the laser used for the observation, so, from the very large spot used to light the sample, the excitating spot took over something that was one thousand times smaller. This is a very simple idea, but it has application in the laser emission.

The above mentioned essential contributions made Prof. Dr. STEFAN W. HELL one of the world's pioneers and leaders in optical nanoscopy, this recognition being confirmed by numerous awards and distinctions, the most prestigious of which was the 2014 Nobel Prize for Chemistry, which he shared with Eric Betzig and William E. Moerner for "**the development of super-resolution fluorescence microscopy**". Stefan Hell was awarded the Nobel Prize after he introduced, in 2000, the concept of STED – stimulated emission depletion in microscopy.

The main argument of the assessment committee who proposes the award of the DHC title at the West University of Timișoara refers to the vast applicability of the devices discovered by Prof. Dr. STEFAN W. HELL, in fields like biology, medicine, materials science, biochemistry, biophysics, optics, physics, nanosciences and nanotechnologies. Talking about the applicability of these discoversies, the President of the Romanian Academy, Academician Ionel Valentin Vlad said:

"The microscope created by Stefan Hell with this extraordinary discovery allows a glimpse into life at the molecular level, into the way cells work, the molecules per se in living cells."

COMISIA DE EVALUARE ȘI DE ELABORARE A LAUDATIO

Preşedinte:

- **Prof. univ. dr. Marilen Gabriel PIRTEA**, *Rectorul Universității de Vest din Timişoara*

Membri:

- **Prof. univ. dr. Viorel Negru**, *Președintele Senatului Universității de Vest din Timişoara*
- **Prof. univ. dr. Nicolae Zamfir**, *Membru al Academiei Române, Director general al Institutului Național de Fizică și Inginerie Nucleară „Horia Hulubei”, Directorul proiectului Extreme-Light Infrastructure - Nuclear Physics (ELI-NP)*
- **Conf. univ. dr. Octavian Mădalin Bunoiu**, *Prorector al Universităţii de Vest din Timişoara*
- **Prof. univ. dr. Daniel Vizman**, *Decan al Facultății de Fizică a Universităţii de Vest din Timişoara*
- **Dr. Daniel Petru Funeriu**
- **Prof. dr. Emmanuel d'Humières,** *cadru didactic universitar la Universitatea Bordeaux, Franța*
- **Prof. univ. dr. habil. ing. Titus Vlase,** *cadru didactic al Facultății de Chimie, Biologie, Geografie a Universității de Vest din Timişoara*

CURRICULUM VITAE

Prof. dr. Dr. h. c. mult. Stefan Walter HELL

Professor,
Director at the Max Planck Institute for Biophysical Chemistry

- 1987 Diploma in Physics, Univ.of Heidelberg (1.0)
- 1990 Doctorate in Physics, Univ. of Heidelberg (summa cum laude)
- 1991 – 1993 Postdoctoral Researcher, EMBL (European Molecular Biology Laboratory)
- 1993 – 1996 Principal Investigator, Laser Microscopy Group; Univ. of Turku, Finland
- 1996 Habilitation in Physics, Univ. Heidelberg; Physics teaching since 02/1996
- 1997 – 2002 Head, Max-Planck Junior Group High Resolution Optical Microscopy, at the Max-Planck-Institute for Biophysical Chemistry Göttingen, Germany
- since 10/2002 Director at the Max Planck Institute for Biophysical Chemistry, Head of Department of NanoBiophotonics
- since 12/2003 Apl. Prof., Faculty of Physics, Univ. of Heidelberg
- since 12/2003 Head of High Resolution Optical Microscopy Division, DKFZ Heidelberg
- since 01/2004 Hon. Prof., Faculty of Physics, Univ. of Göttingen
- 2014 Nobel Prize in ChemistryAwards
- Prize of the International Commission for Optics, 2000
- Helmholtz-Award for metrology, Co-Recipient, 2001
- Berthold Leibinger Innovationspreis, 2002
- Carl-Zeiss Research Award, 2002
- Karl-Heinz-Beckurts-award, 2002
- C. Benz u. G. Daimler-Award of Berlin-Brandenburgisch academy, 2004
- Robert B. Woodward Scholar, Harvard University, Cambridge, MA, USA, 2006
- *"Innovation Award of the German Federal President"*, 2006
- Julius Springer Prize for Applied Physics 2007
- Member of the Akademie der Wissenschaften zu Göttingen 2007
- Gottfried Wilhelm Leibniz Prize, 2008
- Lower Saxony State Prize 2008
- Nomination for European Inventor of the Year of the European Patent Office, 2008
- Method of the year 2008 in Nature Methods
- Otto-Hahn-Preis, 2009
- Ernst-Hellmut-Vits-Prize, 2010
- Hansen Family Award, 2011
- Körber European Science Prize, 2011

- The Gothenburg Lise Meitner prize, 2010/11
- Meyenburg Prize, 2011
- Science Prize of the Fritz Behrens Foundation 2012
- Doctor Honoris Causa of „Vasile Goldiș" Western University of Arad, 2012/05
- Romanian Academy, Honorary Member, 2012
- Paul Karrer Gold Medal, University of Zürich, 2013
- Member of Leopoldina, German National Academy, 2013
- Carus Medal of the Leopoldina, 2013
- Kavli Prize, 2014
- Nobel Prize in Chemistry, 2014
- Romanian Royal Family: Knight Commander of the Order of the Crown
- Romania: Grand Cross of the Order of the Star of Romania, 2015[
- Glenn T. Seaborg Medal
- Foreign associate of the National Academy of Sciences, 2016

The Nobel Prize in Chemistry 2014[1]

Eric Betzig, Stefan W. Hell, William E. Moerner

Stefan W. Hell - Biographical

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I was born on 23 December 1962 in Arad, a medium-sized, ethnically diverse city in the western part of Romania, directly on the border to Hungary. In those days, Romanian, Hungarian and German were the languages that could be heard on the street in a frequent mix, and most locals - including simple folk - spoke two or three of these languages fluently. Ethnic conflicts were unknown, because until 1918 the area was part of the Austro-Hungarian Empire, and linguistic and religious diversity was the normal state of affairs. My parents originated from a place a few kilometres further north, called Santana (German: Sankt Anna), which was founded by German immigrants in the 18th century. Most people in Sankt Anna, including my parents, spoke German as their mother tongue, or, more precisely, a dialect spoken in south-western Germany at that time. This is where I spent most of my childhood.

My father worked as an engineer in a managerial position in a company. My mother was a primary school teacher. Actually she would have liked to study mathematics, but in communist Romania in the 1950s this wasn't possible due to her allegedly 'bourgeois' background. She was expelled from school several times, and only later was she able to obtain her school-leaving certificate with considerable effort. This circumstance, as well as several other calamities that befell the generation of my grandparents in 1945, including ethnically based material dispossession and deportation to Soviet labour camps, eventually led to the view: 'No one can take away what you have learned. And you always carry it with you wherever you go.' Education was about the only asset worth achieving. For this reason, our house was full of books. My parents acquired anything that even remotely seemed interesting. And they liked to travel - but that was only possible within the borders of the country. Nevertheless, we were aware of what was happening outside Romania, as we were well informed from listening to Western radio stations.

My mother being a teacher, who understandably did everything in her power to educate me early, I learned to read at a young age. And because I didn't particularly like kindergarten, she often took me along to her classes. Things were more exciting there. I had no siblings, and I spent many hours with books such as an encyclopaedic lexicon from West Germany, which I studied in detail. I was especially fascinated by things such as the chain reaction, even though I didn't quite understand it. And I still vividly recall watching the moon landing on television which was otherwise full of communist propaganda. But this made the highlights all the more interesting: science fiction thrillers from America that were aired on Sundays in English with Romanian subtitles. That was very exciting, and somehow the aspiration grew in me that I later wanted to become a scientist.

Our classes were held mostly in German, because Romania maintained basic education in all the minority languages. We learned French as a foreign language. In retrospect, I believe I was very fortunate that many of my teachers at the time were in their twenties or thirties and that they were highly motivated to inspire their pupils. I still remember how my chemistry teacher (Figure 1) explained the basic principles of atomic structure in a compelling way, and how amazed I was to learn that most of the atomic mass resided in the much smaller nucleus.

Figure 1. Stefan Hell (top row, 6th from left) with grade eight schoolmates and teachers of the German division of elementary school in Santana, Romania in 1977. Teachers in bottom row: Ms. Martini (mathematics, 2nd from left); Mr. Hans Kling (chemistry, 3rd from right).

After grade eight, at the age of fourteen, I was able to obtain one of the few places at the Nikolaus Lenau Lyceum in Timisoara, one of the best secondary schools in the country. There you could specialise in mathematics and physics, and it was there that I was first propelled towards physics, as I had won a local competition and realised that physics was fun. On the other hand, daily life was difficult, and I associate my time in the school dormitory in Timisoara with going to bed with a grumbling stomach. It was, after all, communist Romania, and Ceausescu was in the process of expanding his dictatorship. The regime in Bucharest - unlike the normal people on the street - was growing increasingly nationalistic and bizarre. The flood of propaganda let the feeling grow that it's not good to live under a dictatorship - especially with a minority background. And it was easy to conclude the latter from my last name.

And another feeling took root in me: things that are publicly asserted and constantly repeated aren't necessarily true. Quite the contrary: I became sceptical about accepted opinions. Coupled with having no prospect of improvement, all this meant that most of the people who could even remotely claim a German or Jewish background tried to leave the country. But that was far from easy.

When a classmate emigrated with her family, I convinced my parents that they too should apply for an exit visa. Besides, my mother had been diagnosed with a disease two years earlier, and one of her doctors recommended emigration to Germany, where she could receive better medical care. After two years of uncertainty and inconvenience with the officials, we were allowed to leave for West Germany with a few belongings. It was on April 8, 1978; I was fifteen. We had no close relatives in Germany and settled in Ludwigshafen, an industrial city west of the river Rhine, far away from the iron curtain. I also found Ludwigshafen to be good, because I had seen

on the map that the university town of Heidelberg was just a few kilometres away, and that struck me as a goal worth pursuing.

I was thrilled about the opportunities in the West, though this was also accompanied by my parents' struggle to settle in Germany. In Ludwigshafen I attended a secondary school, and soon realised that I was far ahead of my classmates in the sciences. I also had a fantastic physics teacher, Mr. Ecker, who gave me great encouragement. Then again, my English was limited to what I had picked up from non-dubbed American and British films in Romania. Finally, I learned that I could graduate from secondary school with only French as foreign language, and I took advantage of a rule that allowed me to graduate one year earlier than usual. I did that and began to study physics at the University of Heidelberg in 1981.

Studying physics was the next great liberation, because the material to study was not dependent on *zeitgeist* or politics. At the same time, the atmosphere in Heidelberg was very conducive. On Friday evenings there was a colloquium, followed by wine and pretzels for all. The first speaker I heard in the colloquium was **Isidor Rabi**. Unfortunately, it wasn't easy for me, because after briefly starting in German, he switched to English at some point. Nonetheless, seeing and hearing one of the greatest scientific minds of the 20th century was an important and highly motivating experience.

I don't know if I stood out as a student. In any case, I was always dissatisfied when I had the impression that the lecturer failed to get to the heart of the matter. I could never accept arguments such as "if you do the maths, you'll know why this is so." I firmly believed that everything could be boiled down to simple principles. And if that wasn't possible, one simply didn't understand the matter. Be that as it may, a consequence of this attitude was that during my studies I spent hours and hours thinking about how I could distil down phenomena and concepts to their essence. During the vacations, I managed to hide out in my room for months - much to the concern of my friends - 'picking apart' textbooks from morning till late and writing my own version of the subject in stacks of notebooks. Some days I only progressed by one or two pages, and it was frustrating when I still hadn't grasped the core of the matter. But it was fantastic to eventually 'discover' what the core was. I was also of the opinion - and it's probably true - that I am terribly bad at memorising things, and if I didn't understand something exactly, I would forget it and fail my oral exams. Fortunately, that did not happen.

Like many physics students, I had planned to specialise in particle or nuclear physics, and Heidelberg was the place to do it. On the other hand, I heard that it was disillusioning to work on large projects and that job prospects were not good. The latter consideration proved decisive, because my father's job was becoming increasingly uncertain, and my mother was again diagnosed with a serious illness. As the time to work on my diploma thesis approached (a final master's thesis lasting up to 2 years), I opted - against my inclination - for a topic which I believed at the time would provide good prospects of finding a job. It was about microlithography, the production of fine structures in photoresist material for computer chips. Professor Siegfried Hunklinger from the Institute of Applied Physics, a low-temperature solid-state physicist who had just moved to Heidelberg from the Stuttgart-based Max Planck Institute for Solid State Research, wanted to

produce piezoelectric surface-wave transducers lithographically and had teamed up with his colleague, Professor Josef Bille, to construct a laser scanner that could be used to write microstructures.

I must have done my diploma thesis work reasonably well, because I was one of the few students Professor Hunklinger planned to keep for doing a PhD. But, for my doctoral thesis, I wanted to focus on something less applied - which wasn't so particular, because most of the other students were concerned with low temperature solid-state physics. Actually, Professor Hunklinger had kind of planned that for me as well, but in the end it turned out to be a subject which again had a touch of applied physics. And I didn't have the courage to say that I would do it with little passion.

As it happened, Professor Bille and Professor Hunklinger had just founded Heidelberg Instruments GmbH, a start-up company developing laser-scanning optical systems for a broad range of applications: optical lithography, ophthalmology, and confocal microscopy for biology, as well as microlithography inspection. Confocal microscopy was about to emerge as a new microscopy technique, having the advantage of suppressing light from above or below the focal plane. In the mid-1980s, it was therefore believed that this could be used to measure transparent 3D photoresist microstructures more accurately, which was important for the mass production of computer chips. My task was to find out if and how this would work. However, that wasn't easy, because the structures on the silicon wafer were transparent and had about the same width and height as the wavelength of light. The confocal principle was not really able to solve the problem; rather it produced complex images that changed drastically with minute changes in the dimensions of the structures. I called the images 'aliens', because they reminded me of the figures of a popular computer game at the time. At first, I wanted to find a mathematical model to predict them, but there were too many process parameters to deal with, and ultimately such an approach would be impractical for a semiconductor manufacturer.

As the only physics graduate student at Heidelberg Instruments, I was more or less on my own. Occasionally, I was able to turn to the company's development manager, Roelof Wijnaendts van Resandt, who had run a group on confocal microscopy at the Heidelberg-based European Molecular Biology Laboratory (EMBL) a few years earlier. But he had little time for me, because the company was struggling to survive. There was also a biology graduate student, Werner Knebel, who was investigating the suitability of confocal microscopy for cell biology. We often talked to each other. I explained to him the physics of image formation and he introduced me to fluorescence imaging in biology. Otherwise, my routine was interrupted only by my walks to the weekly seminars on solid state physics, teaching duties, group meetings, and the colloquia on Friday evenings. I was quite frustrated. Actually, I wanted to do something more exciting than optical microscopy - which I perceived as a boring physics subject of the 19th century, which had nothing to offer apart from diffraction and polarisation.

In the interim, I had received a stipend from a foundation, meaning that I wasn't dependent on the company. I also knew that my thesis advisor was a 'real' physicist with a passion for physics. So I started to ask myself whether there might be an interesting problem left in optical microscopy after all. The only thing that still seemed interesting in my view was the diffraction limit of

resolution. So I figured that breaking this limit would be really new and exciting! All of a sudden, everything looked brighter, because thinking about light microscopy took on a new meaning.

So I decided to pursue the thesis work as initially requested, but what really motivated me was the resolution problem. I knew of course that near-field optical microscopy existed, but it seemed to me like a kind of scanning tunnelling microscopy. In contrast to that, I wanted to come up with a light microscope that looks and operates like a light microscope - but without the limits set by diffraction. So I began to comb through my textbooks again, searching for phenomena suitable for overcoming the diffraction barrier. I pondered all kinds of options from the Stark to the Zeeman effect. I even checked textbooks on nuclear physics. My efforts weren't initially met with success.

But one thing came up most naturally: Virtually isolated from the optics community, I had figured out how to calculate the focal light field at large focusing angles, and had written a computer program to do so. I had solved the problem in my own way and had lots of fun playing around with the field calculations, which worked beautifully. The largest focusing (i.e. aperture) angle of the best objective lenses at that time was around 71°. Of course, I also plugged the theoretically largest value of 90° into my program, which corresponded to a converging hemispherical wavefront. I also calculated what would happen for a complete sphere. While the last two cases were interesting but impractical, it was far more realistic to calculate what would happen if one juxtaposed two lenses with a 71° aperture angle and caused their wavefronts to add up constructively at a common focal point. That the main diffraction peak would become three to four times sharper along the optical axis (z) than with the best single lens was to be expected. However, less obvious was the outcome that the secondary diffraction peaks along the axis were small enough to be discriminated against in a potential image; they would not produce ambiguities or 'ghost images'. So it seemed feasible to improve the resolution along the optic axis by 3–4 fold, by using two counter-aligned ~70° lenses in a coherent manner. That was the idea behind what was later to be called the 4Pi microscope.

Back then I called it the double-lens microscope and presented the results sometime in 1988 in Professor Hunklinger's seminar series - as an addendum to what I was actually supposed to do. The idea was perceived as interesting, but the difficulties in aligning two lenses to focus at the same point and controlling the phase of the wavefronts were thought to be daunting. And, of course, the concept wasn't suitable for silicon wafers - only for transparent specimens such as biological cells. Actually, I set off to try it out, but Heidelberg Instruments disintegrated into several subunits in 1989, and Prof. Hunklinger resigned from it. It is left to be noted that the subunit dealing with confocal microscopy was purchased by the company Leitz which later became Leica Microsystems GmbH, a leading supplier of confocal microscopes.

By the time I had completed my doctoral thesis in the summer of 1990, I was convinced that there must be a way to improve resolution in a more fundamental way. With the two-lens approach I had at least found a beginning, albeit only within the limits imposed by diffraction. But the mindset that I had constructed for myself, picking apart textbooks, told me that physical phenomena must exist that should be suitable to overcome the barrier radically. So much progress

had been made in physics in the 20th century that there had to be at least a single phenomenon that should enable lens-based optical microscopy with resolution at the nanometer scale.

My stipend had run out, and I had asked Professor Hunklinger if I could stay on another year to work on the resolution problem. But optics wasn't his field. It was clear that I would have to go my own way. This wasn't easy because at that time there were no structures in Germany to give young researchers a start. Usually, you needed a professor (mentor) for whom you would work for several years while working towards your *habilitation*, a postdoctoral degree required for having one's own students and to lecture. I neither had such a mentor nor was applying for a postdoctoral position in the USA an option. First, I didn't know anyone there; second, my English was rather modest.

Fortunately, my grandparents, who had meanwhile followed my parents to Ludwigshafen, had saved 10,000 Deutschmarks, which they gave me as a present when I was awarded my doctorate. I sat for a couple of weeks thinking about how I could build a 'double confocal microscope' with two juxtaposed lenses and used the money to pay an attorney to file a patent on it. Since I had worked in the setting of a start-up company, I thought that I may be able to persuade Leica or another big company to support the development. But things worked out differently: Roelof Wijnaendts van Resandt introduced me to his former PhD student Ernst Stelzer, who had succeeded him as head of the microscopy group at the European Molecular Biology Laboratory (EMBL) in Heidelberg. I indicated to Ernst that I wanted to work on the resolution question, and he offered me a stipend for a few months, on the condition that I would apply for external stipends for the rest of my stay. One has to appreciate that at the time there was a surplus of physicists in Germany, and the prospects of doing academic research were poor. However, I had just learned the hard way that it is a mistake not to do what you really enjoy.

I therefore wrote up a small application for a stipend to the German Research Foundation (DFG), the main funding body in Germany. Essentially, I described the double-lens microscope and my view on the prospects of improving the resolution in a lens-based light microscope. Although located in Heidelberg, the EMBL is legally outside Germany, which meant at that time that I could not be funded by the DFG unless my application was formally supported by a German university. Since I could no longer appeal to Professor Hunklinger, I consulted the directory of physics professors at Heidelberg and picked out two whose interests seemed most closely related to the subject.

I wasn't familiar with either of them. One was Reinhard Neumann, a lecturer from Prof. Gisbert zu Putlitz's chair on atom spectroscopy; he asked me whether I wanted to do near-field optical microscopy. I replied with 'far-field only', whereupon he looked at me with a stare. But he read my essay and finally wrote a letter of support. The other was Professor Christoph Cremer, who worked on flow cytometry and chromosome organisation, the only biophysicist in the directory. He also read my little essay with interest. When I came back a few days later, he was excited and showed me a paper that he had published in 1978, which he jokingly referred to as a *jugendsünde*, i.e. a peccadillo of youth. The paper suggested a hypothetical hologram producing a freely propagating elliptical wavefront which was predicted to converge in a single point of light

that would possibly become infinitely sharp, at least much smaller than the diffraction barrier. Scanning this ultrasharp point across the sample was supposed to produce images with resolution well beyond the diffraction barrier. He called it the "4π microscope."

I instantly realized that even if you could build the desired hologram, it would not produce an infinitely sharp point of light. The concept was not congruent with the laws governing the propagation of electromagnetic radiation. But Professor Cremer was supportive too, and wrote the other letter. The stipend was later approved on the condition that I spend six months abroad. I opted for Oxford, to work with Professor Tony Wilson, an early confocal microscopy pioneer. (I finally did that four years later, in 1995.)

The EMBL was a great place. It was international, and the working language was English. I took advantage of this time to learn English, and after I had listened to many presentations, I eventually plucked up enough courage to present in English myself. I had no choice after all. With Ernst Stelzer I had agreed to build the microscope with the two counter-aligned lenses, to see if the axial resolution increase could be realized. It wasn't easy. I remember that in December 1991, one day before my birthday, I had the first clear indication that it was feasible. The key was that I could exactly predict what the experimental data should look like, so I was able to discriminate against misalignment. In the publication, Ernst suggested that we call it the "4π microscope," which I wasn't particularly happy about. For one thing, the solid angle of the double lens arrangement was far from 4π. Furthermore, the actual discovery was that '4π' wasn't needed to increase the axial resolution; two high-angle lenses were sufficient. Moreover, the Cremer paper had drawn an improper physical conclusion (i.e. a point-like spot of light) and had completely missed the axial resolution increase as the actual benefit of adding the other side of the solid angle. Ernst and I finally compromised not to use the Greek letter π, but the Roman letters Pi. Whether I liked it or not, the name 4Pi stuck. The group was later reinforced by two talented physics diploma students, Gernot Reiner and Steffen Lindek. Since Ernst did not have the *habilitation*, the thesis works were officially handled by Professor Cremer, who became increasingly interested in the resolution topic.

In this quest for increasing axial resolution using two lenses, it was not enough to produce a focal interference pattern with counter-propagating waves. The challenge was to create a main focal diffraction peak with negligible secondary ones, i.e. an optical transfer function of the microscope that was both expanded and contiguous along the optic axis. Otherwise, one would end up with image artefacts. With the use of the two-photon excitation modality introduced in microscopy by Winfried Denk and colleagues, making contiguous transfer functions became reliably possible. But there were still no images of biological specimens taken and, of course, using two opposing lenses didn't break the diffraction barrier. The latter particularly vexed me. However, the good thing was that the resolution question in far-field microscopy had been raised for all to see, and, importantly, I had a foot in the door.

Ernst Stelzer and I ended up with very different views on how realistic it would be to overcome the diffraction limit. We parted ways in 1993. He went on to tilt two low-angle lenses

so that they were at almost 90° to each other and called it confocal theta microscopy. Later he refined this arrangement into what is now called the light-sheet microscope.

In the spring of 1993, the stipend ran out, and I could no longer stay at the EMBL. The DFG, which had just set up a special funding program called 'New Microscopy for Biology and Medicine', told me that I couldn't apply for research funds because I had no job and no laboratory to work in. They funded a couple of near-field optical microscopy projects though.

But once again I was lucky: Also working in the Stelzer group was a Finnish colleague, Pekka Hänninen, who planned to return to Finland. Pekka had realised the timeliness of the resolution topic and introduced me to his future professor, Erkki Soini of the University of Turku, who offered to submit a research proposal on 4Pi microscopy to the Academy of Finland, basically on my behalf. The Academy agreed to fund the project, on condition that I worked in Turku. So I arrived in Turku in the summer of 1993, and Erkki Soini, Pekka, and I worked very hard to set up a small optics laboratory. We started where I had left off at the EMBL, namely with 4Pi microscopy - first, because it was the only tangible approach at the time, and second because the credibility of the whole endeavour was at stake. Rumour was that my efforts would end up like all other far-field optical 'superresolution' efforts before, namely as an academic curiosity. The situation was not helped by the fact that Ernst Stelzer started to distance himself from the '4Pi' work carried out in his laboratory in publications.

At the same time, I felt that simply changing the way light is focused or re-arranging lenses will not change matters fundamentally. The only way to do so would be either via some quantum-optical effects or - what appeared more promising - via the states of the molecules to be imaged. The molecules whose states could be most easily played with were fluorescent ones, which, fortunately, were also those of interest in the life sciences.

On a Saturday morning in the fall of 1993 I was browsing through Rodney Loudon's book on the quantum theory of light in the hope of finding something suitable. A few weeks earlier I had imagined what would happen if the fluorescent molecules would be re-excited from the excited state using slightly offset beams. When my eyes caught a chapter dealing with stimulated emission, it dawned on me: Why excite the molecules, why not de-excite them, i.e., keep them non-fluorescent in order to separate them from their neighbours. I was electrified by the thought and immediately checked Fritz Schäfer's book on dye lasers to see what was reported about the stimulated emission of fluorophores such as rhodamines. A quick assessment showed that an image resolution of at least 30–35 nanometres could be achieved in the focal plane, i.e. 6–8 times beyond the diffraction barrier. That was amazing. It was also instantly clear that the achievable resolution only depended on the intensity the sample would tolerate, and in principle was unlimited.

What also intrigued me was the fact that the resolution could be obtained without *a priori* assumptions about the distribution of features to be imaged. This was because at that time, it was widely believed that the route towards higher resolution in the far-field was data processing, which typically required some assumptions about the object. However, in my case, mathematical processing was not needed. The concept was based just on the use of a basic state transition, i.e.

"just on physics." I finally had an example of the type of approach I had been seeking for. It was the concept of STED microscopy.

But it wasn't so easy to test this idea in Turku. I also thought that a tunable dye laser would probably be needed to optimise for de-excitation. But there was no dye laser to be had far and wide. After explaining the concept to Pekka, Erkki and other friends in the laboratory, I called up a former student friend from the Hunklinger laboratory in Germany, Leonore Hornig, who had become a patent attorney in the interim. I explained the idea to her and briefed her on filing a patent. I also felt that I should publish the idea in theoretical terms in such a way that it was as close as possible to reality and therefore hard to challenge. Before I left Heidelberg, Jan Wichmann, a physics student whom I knew privately, had expressed his desire to come to Turku for two weeks in December to work with me as an intern after finishing his diploma work with Prof. Jürgen Wolfrum. I explained the concept to him and asked him to model it numerically to be sure that the numbers were as close as possible to a real experiment. Jan's preference was to use Gaussian beams because those could be handled relatively easily by the algebraic program *Mathematica*. The numerical evaluations of the rate equations largely coincided with my initial assessments. In any case, the paper proposing STED microscopy eventually read like a recipe: it was full of numbers. I tried hard to omit anything that could be interpreted as an oversimplification or exaggeration, because, not having a mentor and knowing that it was just a theoretical proposal, I was very much concerned about a total rejection.

On the other hand, the paper was written to convince the community that nanoscale far-field fluorescence microscopy is viable, as well as in the hope of getting a job and the funds to do it. Whether I would ever be able to realise it myself was indeed doubtful at that time, because the Finnish Academy grant was gradually nearing its end. Yet, in retrospect, I must say that the time in Finland was really exciting and decisive (Figure 2).

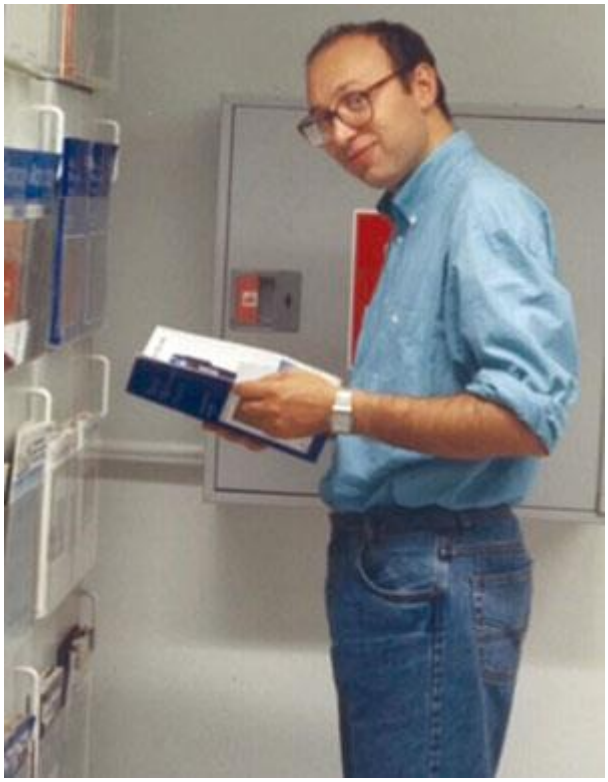

Figure 2. Stefan Hell at the Department of Medical Physics in Turku, Finland in 1993, at about the time of conception of STED microscopy.

I also quickly realised that stimulated emission is not the only state transition that can be used to the same end. After all, the basic idea was to ensure that a part of the features illuminated by the excitation light remain briefly dark so that they can be separated from other features residing within the diffraction range. So I had the idea of parking the fluorophores in a dark metastable state, something dye laser operators were trying to avoid at all costs. This also had the important benefit of requiring less intense light. Since all my papers were published in specialised optics journals - which didn't make my CV look particularly impressive - I submitted this proposal to a more general physics journal. When I received no response after months, I mustered all my courage and called the editor, who happened to be German. He told me that he had doubts about whether the diffraction limit could actually be overcome. He had sent the manuscript to three experts in near-field optical microscopy (!) - among them a famous one in the USA - and only one of them had replied. The reply was not favourable. It would all have to be demonstrated experimentally before making such claims, the editor said. When he realised my despair and that I didn't really have the means to do that, he advised me to go back to Professor Hunklinger, so that he submits an application to the DFG on my behalf. I was terribly disappointed about the German academic system.

Today, it's perhaps hard to understand, but the 1990s were not particularly receptive to the notion of obtaining nanometre-scale resolution in a lens-based optical microscope. This can be readily concluded from the fact that no laboratory had tried STED, although I had advocated the

concept with much passion since April 1994. In my opinion, there were two reasons for this. First, near-field optical microscopy seemed the way to go at the time, including for the life sciences. Eric Betzig, who worked at Bell Laboratories in the early 1990s, had published prominent papers, such as a *Science* paper in 1993, showing the near-field optical recording of single molecules at room temperature. The second reason was probably even weightier. In the 20th century, various people had repeatedly proposed concepts to overcome the diffraction barrier in the far-field, most prominently Toraldo di Francia and Lukosz. Yet, none of these concepts were practical, or got beyond a factor of two. So it was therefore natural not to take a far-field method like STED and related ideas seriously either.

I was convinced that this time it would be different. My reasons were simple: STED fundamentally differed from other concepts in that it relied on separating features via the molecular states of the sample, rather than on tackling diffraction itself. But even more importantly, I could not find a basic physical oversight in my concept - in contrast to all of the ones reported until then. If problems were encountered in the realisation, they would only be technical, not conceptual in nature, which meant that they could be overcome through development. With the right transitions, one can transfer fluorophores between two states, such as a bright and a dark state, as one likes. When the molecule is in a dark state, that doesn't mean that the (fluorescence) signal is lost; it simply isn't produced. In other words, you can discern adjacent molecules by keeping some of them silent without losing anything, except time. If some signal is nevertheless lost, that is not due to the approach, but to the fact that something else takes place as well - something that is outside the conceptual framework. By discriminating against that, one can make the concept work. This insight gave me the courage to carry on with the development.

However, a first research proposal submitted from Turku in 1995 to a European grant agency with a view to implementing STED was rejected. But fortunately, a Marie Curie individual postdoctoral stipend came through at the last minute. In this precarious situation, Prof. Soini advised me to license my 1990 privately owned patent for the double-lens microscope (a.k.a. the 4Pi) to a company in Turku, Wallac Oy, in exchange for research funding. The company's CEO agreed to transfer 100,000 dollars to a university account. To this day, I believe that compassion played a role.

Those funds were crucial, because they bought me time for a very fortunate event in my life: Dr. Thomas Jovin, the Managing Director of the Max Planck Institute for Biophysical Chemistry in Göttingen at the time, had become aware of my activities. An accomplished and open-minded scientist with Ameri- can background, who successfully kept abreast of the latest developments in molecular biology, fluorophore chemistry, and optics alike, he convinced Erwin Neher, Herbert Jäckle, Peter Gruss, Klaus Weber, Jürgen Troe and the other directors of the institute, to invite applications for setting up a small microscopy research group for five years. They had Winfried Denk (then at Bell Labs) or me in mind. In the spring of 1996 I spoke to Winfried on the phone. When he said that he wasn't interested in this type of non-tenure track position, it came as a big relief. I had a good chance of securing the job.

In the meantime, we had made progress with STED microscopy in Turku. After testing a few dye solutions in a cuvette with Ignacy Gryczynski of Joseph Lakowicz' group in Baltimore that showed some fluorescence modulation, I found out that one could apply a heavily chirped Titanium Sapphire laser to turn off a dark red fluorophore (with the trade name Pyridin2) under microscopy conditions almost completely. This was not easy to work out, because unlike in a cuvette, in a microscopy sample, stirring is not an option to get rid of radicals and bleaching, and the intensities are by orders of magnitude higher. It was also difficult to demonstrate the resolution increase directly, because Pyridin2 could not be coupled to biomolecules. Fortunately, it occurred to me how it could be done indirectly: slightly offsetting the STED beam with respect to the excitation beam was expected to reduce the focal fluorescence region to subdiffraction dimensions. Translation of a confocal point detector across the image plane then proved that this reduction indeed occurred. The measurements were done together with a diploma student, Franziska Meinecke, in 1995. From that point on, I knew that STED microscopy would work - at least under certain conditions. Franziska was less optimistic. She gave up science finally, saying that she felt sorry for me: difficult research subject, little support, no real prospects, and lots of sacrifices. It was sobering to hear that from a student, but I decided to carry on.

I didn't write up those initial STED results because I thought that it may end up in a low-ranking journal again. However, in January 1996, I showed the data at the Friday physical colloquium in Heidelberg, where I gave a talk in front of my former professors including Otto Haxel, Franz Wegner, Joachim Heintze, and Dirk Schwalm, who asked questions at the end. It was my *habilitation* lecture, and *habilitation* was important to carry on in science and supervise one's own diploma and PhD students (officially). Until then, Professor Cremer was taking care of the formalities. He thus also became co-author of some of the papers and advised me how to steer clear of political issues during the *habilitation* process. Today, I am very grateful that the physics faculty allowed me to habilitate in Heidelberg despite the fact that all the work was done in Turku. But contrary to many public assertions, I never was a student or a postdoc of Prof. Cremer. Nor did I work under his intellectual guidance. Rather the relationship reflected in part the inability of the German academic system of the 1990s to provide true indepencence to young researchers.

In December 1996 I took up the position in Göttingen. It was just in the nick of time, as the money from Wallac Oy had run out. The Max Planck Institute in Göttingen was incredible because, for the first time, I was able to plan a little ahead and submit my own research proposals. I submitted a grant for STED to an agency of the German Federal Ministry of Research, which was promptly rejected. However, the officials in charge accepted my appeal and approved the grant against the scientists' recommendations. Shortly thereafter, Thomas Klar applied to work as a doctoral student in my laboratory. Thomas grasped the STED concept quickly and was exceptionally talented. Combined with the much better equipment now available, in a few months we reproduced and outperformed the experiments carried out in Turku. 4Pi microscopy had meanwhile yielded compelling images, too.

In 1999 Stefan Jakobs joined in as the first biologist postdoc, greatly extending the group's interdisciplinary expertise. He had realised that the resolution was undergoing a transition and was

attracted by the idea to pioneer its use in the life sciences. We were thus able to show beyond a doubt that the resolution of far-field fluorescence microscopy can be drastically improved, and also used in biological imaging. The paper was initially written up for the journal *Nature*, which decided not to send it out for review. I resubmitted it to *Science*, where it had the same fate.

Eventually, it got published in the *Proceedings of the Natural Academy of Sciences of the U.S.A.* in 2000. This time we had been more fortunate. As we learned later, the manuscript ended up with Shimon Weiss of the Lawrence Berkeley National Lab, who had participated at a symposium a couple of months earlier, where I had presented the data for the first time. He and the other reviewers accepted the paper and Shimon wrote a commentary in *PNAS* pointing out its implications. Given its history, it was very pleasing to see this paper being highlighted in Prof. Måns Ehrenberg's presentation of the 2014 Nobel Prize in Chemistry.

The year 2000 was also fortunate in another aspect: I married my wife, Anna, a pediatric orthopaedic surgeon at the Göttingen university hospital, whom I had met in Göttingen in 1997.

In 2002, to my surprise, the Max Planck Society offered me scientific membership at the Göttingen Institute, which meant tenure and a stable funding contribution to my science.

Since 1994 it had been clear that any reversible transition between a fluorescent and a non-fluorescent molecular state is a possible candidate for overcoming the diffraction limit. In fact, everyone in my laboratory was instructed to keep eyes open for unexpected ways to modulate the fluorescence capability of a molecule. It was also clear that resorting to reversible on-off-transitions with long-lived state pairs would reduce the intensities required to overcome the diffraction barrier.

The intensity issue was often cited against STED. Therefore, in 2003, to make chemists and fluorescent protein designers aware of the transformative potential of such on-off state transitions for microscopy, I wrote up a little communication to *Nature*. The communication highlighted the - in my view - historical opportunity to design switchable fluorescent markers for the purpose of breaking the diffraction barrier.

This time, *Nature* sent out the communication for review, but all three reviewers rejected the paper outright, in fact with improper arguments and contentions. In my view, the actual reason for rejection was that "experts" in the fluorescence microscopy field did not (want to) accept that the resolution was about to undergo a historical change. And **they did not understand that the fluorescent molecules were the key players in this change**. They rather saw the field centred around multiphoton excitation, fluorescence lifetime imaging, and single-molecule detection, which no doubt were important, too. In any case, the paper ended up in *Appl. Phys. A*, where it was seen only by those who screened explicitly for it. Later, I asked myself what would have happened if the power of using photoswitchable molecules would have become apparent to the greater chemistry and biology community much earlier.

In this situation, I felt that I had to advance photoswitchable fluorophore synthesis myself, which wasn't so easy since organic chemistry and molecular biology was not my background. So, I expanded the laboratory to include organic chemistry (with Vladimir Belov), and switchable fluorescent protein development (with Stefan Jakobs). This allowed me to follow a more

systematic approach for playing the "on-off game," harnessing other state transitions as well, such as cis-trans isomerisation. The STED idea could thus be expanded to encompass other state transitions, and particularly to operation at low light levels (RESOLFT). Therefore, starting from 2003 I strongly advocated the development and use of photoswitchable fluorescent proteins and organic fluorophores, because I felt that they would have the potential to provide the ultimate solution to the resolution problem in fluorescence microscopy.

STED 'proper' progressed as well. In 2003 we reported the first nanoscale far-field immunofluorescence images using STED. There were still hurdles to overcome. But many could be taken one by one - or the technological developments around us worked to our advantage.

In early 2004 my mother passed away in Ludwigshafen, after a twenty-year battle against cancer. At around the same time, I also started to set up a small group at the German Cancer Research Center (DKFZ) in neighbouring Heidelberg to give researchers in this field direct access to the novel developments in microscopy.

In the same year, the Howard Hughes Medical Institute (HHMI), a large philanthropic organisation in the USA, started to set up Janelia Farm Research Campus, a new type of institute where scientists are given ample resources and freedom to concentrate on important scientific problems. In 2004, HHMI and the Director of Janelia Farm, Gerald Rubin, asked the Max Planck Society and other organisations to help identify important problems to work on. I took part in two symposia for identifying such research topics, one of which I organised together with another Max Planck Society member in Munich. At this meeting, superresolution fluorescence microscopy was represented by myself and Mats Gustafsson, a spectacular Swedish colleague from the University of California at San Francisco. Mats had joined the field in about 1996–97 by introducing a widefield version of the two-lens ('4Pi') arrangement. A hallmark of Mats's approach was to describe resolution and image formation in the spatial frequency domain. In fact, I never met a person who could think in frequency space as effectively as Mats. While I had not excluded obtaining superresolution in a widefield layout, I had felt that it would be easier to overcome the diffraction barrier first in a single-spot arrangement. This thinking was not wrong, but Mats advanced much further with widefield camera-based layouts than I and anyone else would have imagined. This applied not only to axial but also to lateral resolution improvements. He was of historical calibre.

Mats and I were about the only ones pushing far-field optical superresolution in those days. At scientific meetings we would present our latest data right from the optical table - usually many months before submission. This aspect gave the meetings a certain flavour - to the point of occasionally being marked somewhat by our friendly competition. This applied also to the HHMI-Max- Planck meeting in Munich. It then became obvious to anyone that far-field superresolution fluorescence microscopy was a hot topic. It is left to be noted that Mats was later hired to Janelia Farm and sadly passed away in 2011 after having left a huge legacy in microscopy.

In 2005 I received a very complimentary email from Eric Betzig saying he was entering the superresolution field again, attracted by my and Mats's work. I had not met him personally, but I was aware of his eminent role in near-field optics in the early 1990s. However, this time Eric set

out to work in the far-field. In fact, I had been asked by Janelia Farm seniors whether I felt Eric could still make a difference. I was very confident about that, given his accomplishments in near-field optics. And this turned out to be true, when I heard from him again about a year later.

In 2005, my wife Anna gave birth to our twin boys Sebastian and Jonathan.

The year 2006 was to become an *annus mirabilis* for the field. In 2005 my group had carried out three studies demonstrating for the first time that far-field superresolution fluorescence microscopy was able to give new insights in biology, (e.g. with Katrin Willig, Silvio Rizzoli, Thorsten Lang and Robert Kellner); they were published in early 2006. In this context, I am particularly grateful to my colleague Reinhard Jahn and Stephan Sigrist, now a professor in Berlin, who came up with interesting biological questions. In 2006, the development of the first commercial STED microscope was also completed. And, importantly, Eric Betzig and Harald Hess first realised and presented another major concept for far-field super-resolution, called PALM. Unlike STED or RESOLFT which briefly switched the fluorophores off using a pattern of light, PALM followed a 'bottom-up' approach: the molecules of the features to be resolved were stochastically and individually switched on and off, followed by localisation for position determination.

The art of detecting individual molecules had been pioneered by W.E. Moerner and Michel Orrit and had co-existed with far-field superresolution imaging for about 15 years. Superresolution and single-molecule detection were in fact two different fields, each having their own dynamics and proponents. For example, until 2006, single molecules had been used in superresolution microscopy for testing the resolution only. The systematic use of on-off-switching for separating molecules individually in a spatially stochastic manner, as first done in PALM, added a new dimension to superresolution fluorescence microscopy.

Eric's work became public slightly before identical concepts were published by the groups of Xiaowei Zhuang (Harvard) and Sam Hess (U Maine), who called them STORM and FPALM, respectively. One year earlier, the groups of Paul Selvin (Urbana-Champaign), Nobert Scherer (Chicago), and Rainer Heintzmann (King's College London) had come very close to this concept as well, bearing witness to the fact that, in 2005, far-field fluorescence nanoscopy was no longer an exotic topic. In any case, the works published in 2006 by Eric, who meanwhile had moved to Janelia Farm, Xiaowei Zhuang, Sam Hess and their teams gave the field an enormous boost.

'Superresolution' fluorescence microscopy or 'nanoscopy' as we understand it today, fundamentally differs from the diffraction-limited one in that the separation of adjacent structural details is not accomplished just by focusing the light in use, but through the transient occupation of two different molecular states. In my view, this principle is so fundamental that it offers many opportunities to develop a whole range of powerful superresolution variants. I am delighted to see how this field is unfolding and how it is advancing the life sciences as well as other areas.

While 4Pi microscopy did not overcome the diffraction barrier *per se*, both STED-like and stochastic single-molecule-based variants of subdiffraction resolution fluorescence microscopy have now been implemented with '4Pi' arrangements in order to provide the largest axial and hence

3D-resolution possible. Meanwhile all major microscope manufacturers offer 'superresolution' microscopes as their flagship products.

In 2009 our daughter Charlotte was born. We are so grateful for having three wonderful children who enrich our lives and give us huge inspiration and motivation for the work that we do.

In September 2014, I shared, with Thomas Ebessen and Sir John Pendry, the 2014 Kavli Prize in Nanoscience. The celebrations in Oslo were highly memorable for me, my wife and the children. As it turned out a month later, they were actually an exquisite "practice" for my family since another big event was to come. On October 8, I was informed by the Secretary of the Royal Swed- ish Academy, Prof. Staffan Normark, that I would share the 2014 Nobel Prize in Chemistry with Eric Betzig and W.E. Moerner. The Nobel week was a truly unique experience not only for my family but also for many members of my group and friends who joined us in Stockholm.

I was fortunate over the years to be accompanied by further outstanding students and postdoctoral scientists who have joined this quest, each making important contributions: Martin Schrader, Alexander Egner, Andreas Schönle, Jörg Bewersdorf, Volker Westphal, Lars Kastrup, Jan Keller, Gerald Donnert, Johann Engelhardt, and Christian Eggeling, to name just a few. Although the work done by my colleagues and myself has received the utmost recognition, there is still much to be done, and I still have a lot of passion contributing to the advancement of this field.

Today, now co-responsible for the new generation of scientists, I often wonder whether the way in which science is organised sufficiently encourages young researchers to pursue unusual research topics. So far I have kept myself well out of administrative duties and science policy-making - to the delight of my group, but not always that of my colleagues. But one thing remains close to my heart: I have recently launched an initiative to explore new ways of helping young researchers to embark on risky projects at an early stage of their career. And since many of my colleagues in the Max Planck Society also find this idea very interesting, I am optimistic that this endeavour will work out as well.

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