## **Content**

List of contributing authors—V		
Introduction—1		
Keith Mo	offat, Feng Zhang, Klaus Hahn, Andreas Möglich	
1	The biophysics and engineering of signaling photoreceptors — 7	
1.1	Photoreceptors — 7	
1.1.1	Novel photoreceptors —— 10	
1.1.2	Biophysics of photoreceptors and signal transduction——10	
1.2	Engineering of photoreceptors—12	
1.2.1	Approaches to designing light-regulated biological processes ——13	
1.3	Case study – transcriptional control in cells by light —— 17	
1.4	Conclusion—18	
	Acknowledgements—20	
	References —— 20	
Kally A	Talagualus Liaf F. Fanna Kaul Daiasassath	
	Zalocusky, Lief E. Fenno, Karl Deisseroth	
2.1	Current challenges in optogenetics—23 Introduction—23	
2.2	Background: current functionality of tools—23	
2.3	Unsolved problems and open questions: technology from cell biology,	
	optics, and behavior—25	
2.4	Unsolved problems and open questions:	
	genomics and biophysics——28	
2.5	Conclusion—31	
	References —— 33	
Ehud Y. I	sacoff, Richard H. Kramer, Dirk Trauner	
3	Challenges and opportunities for optochemical genetics —— 35	
3.1	Introduction—35	
3.2	Photosensitizing receptors — 36	
3.3	PCL and PTL development and applications—39	
3.4	Advantages and disadvantages of PCLs and PTLs —— 41	
3.5	Conclusion—42	
	References—42	
Thomas	V~~~f~l	
Thomas	•	
	Optogenetic imaging of neural circuit dynamics using voltage-sensitive	
	fluorescent proteins: potential, challenges and perspectives—47	
4.1	Introduction—47	
4.2	The biological problem——47	



4.3	The large scale challenge of circuit neurosciences—47
4.4	The current approach to the large-scale integration problem —— 48
4.5	Large-scale recordings of neuronal activities using optogenetic approaches ——49
4.6	Genetically encoded voltage indicators: state of development and application——49
4.7	Unsolved methodological / technical challenges——52 References——52
Gero M	iesenböck
5	Why optogenetic "control" is not (yet) control—55
	Acknowledgments —— 59
	References — 59
Mario d	de Bono, William R. Schafer, Alexander Gottschalk
6	Optogenetic actuation, inhibition, modulation and readout for neuronal
	networks generating behavior in the nematode Caenorhabditis
	elegans—61
6.1	Introduction – the nematode as a genetic model in systems
	neurosciencesystems neuroscience—61
6.2	Imaging of neural activity in the nematode——62
6.2.1	Genetically encoded Ca <sup>2+</sup> indicators (GECIs)—— <b>62</b>
6.2.2	Imaging populations of neurons in immobilized animals—62
6.2.3	Imaging neural activity in freely moving animals—63
6.2.4	Other genetically encoded indicators of neuronal function—64
6.3	Optogenetic tools established in the nematode —— <b>64</b>
6.3.1	Channelrhodopsin (ChR2) and ChR variants with different functional
	properties for photodepolarization——64
6.3.2	Halorhodopsin and light-triggered proton pumps for
	photohyperpolarization——65
6.3.3	Photoactivated Adenylyl Cyclase (PAC) for phototriggered cAMP-
	dependent effects that facilitate neuronal transmission—65
6.3.4	Other optogenetic approaches — 66
6.3.5	Stimulation of single neurons by optogenetics in freely behaving
	C. elegans <b>——66</b>
6.4	Examples for optogenetic applications in <i>C. elegans</i> —68
6.4.1	Optical control of synaptic transmission at the neuromuscular junction
	and between neurons——68
6.4.2	Optical control of neural network activity in the generation of
	behavior——69
6.5	Future challenges —— 70

6.5.1	Closed-loop optogenetic control and optical feedback from behavior and individual neurons — 70		
6.5.2	Requirements for integrated optogenetics in the nematode ——72 References ——74		
Matt L.	Matt L. Labella, Stephan Sigrist, Erik M. Jørgensen		
7	Putting genetics into optogenetics: knocking out proteins with light—79		
7.1	Introduction—79		
7.2	Protein degradation—79		
7.3	Light stimulation —— 85		
	References —— 88		
André F	iala		
8	Optogenetic approaches in behavioral neuroscience—91		
8.1	Introduction—91		
8.2	Approaches to dissect neuronal circuits: determining physiological		
	correlations, requirement and sufficiency of neurons—92		
8.3	Optogenetic analysis of simple stimulus-response-connections ——93		
8.4	Optogenetic and thermogenetic analysis of modulatory neurons:		
	artificial mimicry of relevance——95		
8.5	Conclusion——97		
	References — 97		
Fumi Kı	ıbo, Herwig Baier		
9	Combining genetic targeting and optical stimulation for circuit dissection in		
	the zebrafish nervous system ——101		
9.1	Introduction——101		
9.2	Zebrafish neuroscience: Genetics + Optics + Behavior——101		
9.3	Genetic targeting of optogenetic proteins to specific neurons——102		
9.4	Optical stimulation in behaving zebrafish——103		
9.5	Annotating behavioral functions of genetically-identified neurons by		
	optogenetics——103		
9.5.1	Spinal cord neurons (Rohon-Beard and Kolmer-Agduhr cells)——103		
9.5.2	Hindbrain motor command neurons —— 104		
9.5.3	Tangential neurons in the vestibular system——104		
9.5.4	Size filtering neurons in the tectum —— 105		
9.5.5	Whole-brain calcium imaging of motor adaptation at single-cell		
	resolution——105		
9.6	Future directions —— 106		
	References—106		

	G. Oertner, Fritjof Helmchen, Luis de Lecea, Heinz Beck, Arthur Konnerth, in Kaupp, Thomas Knöpfel, Hiromu Yawo, Michael Häusser
10	Optogenetic analysis of mammalian neural circuits —— 109
10.1	Introduction—109
10.2	Optogenetic approaches to probe integrative properties at the cellular level——110
10.2.1	Excitatory signal integration at dendrites——110
10.2.2	Control of excitatory signal integration by inhibition or
	neuromodulation——111
10.2.3	Long-term analysis of synaptic function——113
10.3	Circuits and systems level——114
10.4	Optogenetics and behavior: testing causal relationships in freely
	moving animals——120
	References——121
Viviana	Gradinaru
11	Optogenetics to benefit human health: opportunities and
	challenges——127
11.1	Introduction——127
11.2	Opportunities for translational applications—127
11.3	Safety challenges —— 129
11.4	Need for feedback —— 130
11.5	Conclusion——130
	References——130
Edward	S. Boyden
12	Optogenetic tools for controlling neural activity: molecules and
	hardware——133
12.1	Overview——133
12.2	Molecular tools for sensitizing neural functions to light——133
12.3	Hardware for delivery of light into intact brain circuits——136
	References —— 137
Ada Eb	an-Rothschild, Clara Touriño, Luis de Lecea
13	In vivo application of optogenetics in rodents——143
13.1	Introduction —— 143
13.2	Sleep / wake regulation——143
13.3	Addiction——145
13.4	Fear, anxiety and depression——148
13.5	Autism and schizophrenia——150
13.6	Aggression——150
13.7	Breathing——151

13.8	Seizures——151
13.9	Conclusion—152
	Acknowledgments——152
	References —— 152
V. Sturm	
14	Potential of optogenetics in deep brain stimulation ——157
14.1	DBS history and indications——157
14.2	Electrical DBS: advantages and drawbacks——157
14.3	Potential of optogenetic stimulation——158
14.4	Conclusion—159
	References —— 159
Zhuo-Hu	a Pan, Botond Roska, José-Alain Sahel
	Optogenetic approaches for vision restoration — 161
15.1	Introduction——161
15.2	Proof-of-concept studies——162
15.3	Light sensors — 164
15.4	rAAV-mediated retinal gene delivery—166
15.5	Retinal cell-type specific targeting —— 167
15.6	Summary—— <b>169</b>
	References — 169
	Further reading —— 171
Eberhart	Zrenner, Birgit Lorenz
	Restoration of vision – the various approaches —— 173
16.1	Introduction—173
16.2	The various conditions to be treated —— 173
16.3	State of the various restorative approaches — 174
16.3.1	Neuroprotection—174
16.3.1.1	Encapsulated cell technology (ECT) — 174
16.3.1.2	Electrostimulation—175
16.3.1.3	Visual Cycle modulators——175
16.3.1.4	Gene replacement therapy — 176
16.3.1.5	Stem cell approaches——176
16.3.1.6	Optogenetic approaches —— 177
16.3.1.7	Electronic retinal prosthesis——177
16.3.2	Cortical prosthesis — 181
16.3.3	Tongue stimulators—— <b>181</b>
16.4	The current situation——182
16.5	Open Questions ——182

16.6	Conclusion—183
	References —— <b>183</b> Selected registered clinical trials as by February 2013 —— <b>185</b>
Tobias Mos	er
17 Op	togenetic approaches to cochlear prosthetics for hearing
res	storation—187
17.1	Background and state of the art—187
17.2	Current research on cochlear optogenetics — 189
17.2.1	Current and future work on cochlear optogenetics aims at—190
17.3	Potential and risks of cochlear optogenetics for auditory
	prosthetics——190
	References —— 191
Sabine Sch	leiermacher
18 His	story in the making: the ethics of optogenetics——193
	References—199
Henrik Wal	ter, Sabine Müller
19 Op	togenetics as a new therapeutic tool in medicine? A view from the
pri	nciples of biomedical ethics—201
19.1	Principles of optogenetics—201
19.2	Principles of biomedical ethics—202
19.2.1	Respect for the patient's autonomy—205
19.2.2	Nonmaleficence—206
19.2.3	Beneficence—207
19.2.4	Justice——208
19.3	Conclusion—209
	References——210
Appendix:	Dahlem-Conference (Berlin, September 2–5, 2012): "Optogenetics.
••	Challenges and Perspectives."—213
Index2	-