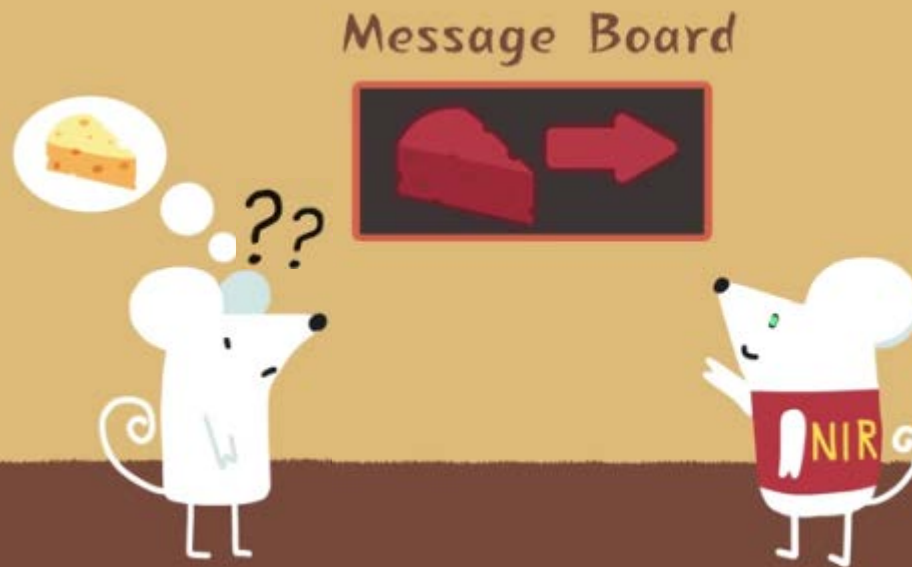


# Upconversion Nanoparticles (UCNPs) in Neuroscience



Journal Club, 16th April 2019

Alexandra Bentrup

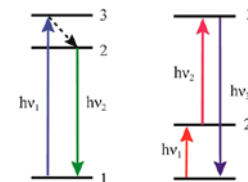
# Photon upconversion (UC)

CHEMICAL  
REVIEWS

Review  
pubs.acs.org/CR

Upconversion Luminescent Materials: Advances and Applications

Jing Zhou,<sup>†</sup> Qian Liu,<sup>†</sup> Wei Feng, Yun Sun, and Fuyou Li\*

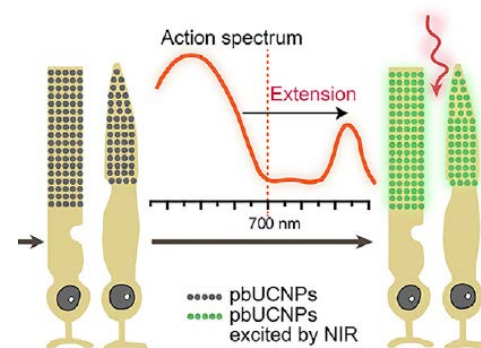


## Article

### Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae

Yuqian Ma,<sup>1,5</sup> Jin Bao,<sup>1,2,5,\*</sup> Yuanwei Zhang,<sup>3,5</sup> Zhanjun Li,<sup>3</sup> Xiangyu Zhou,<sup>1</sup> Changlin Wan,<sup>1</sup> Ling Huang,<sup>3</sup> Yang Zhao,<sup>3</sup> Gang Han,<sup>3,\*</sup> and Tian Xue<sup>1,2,4,6,\*</sup>

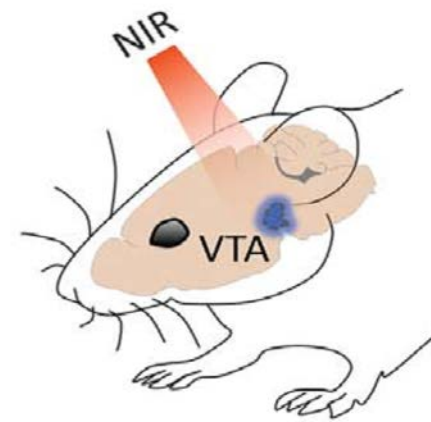
Cell



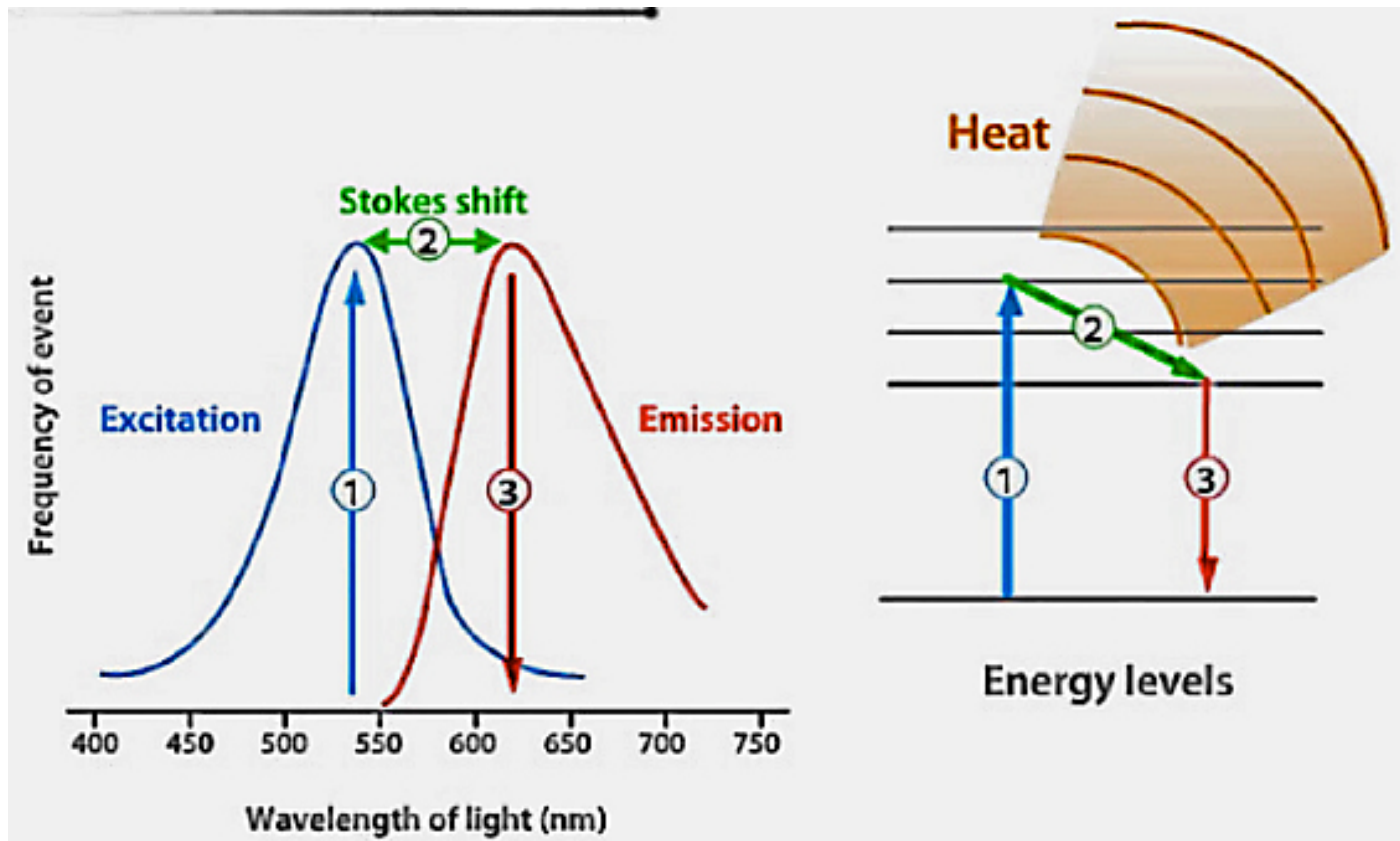
## NEUROSCIENCE

### Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics

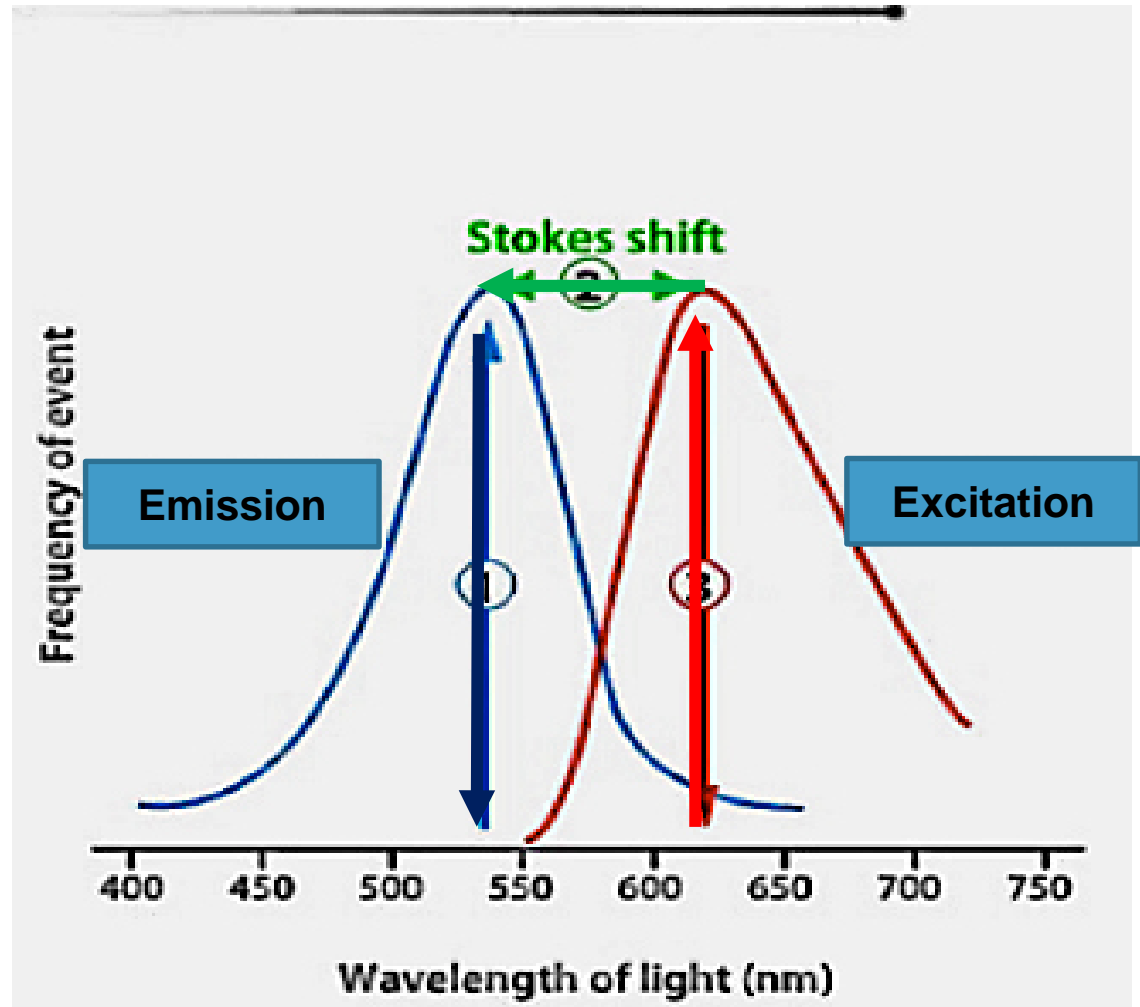
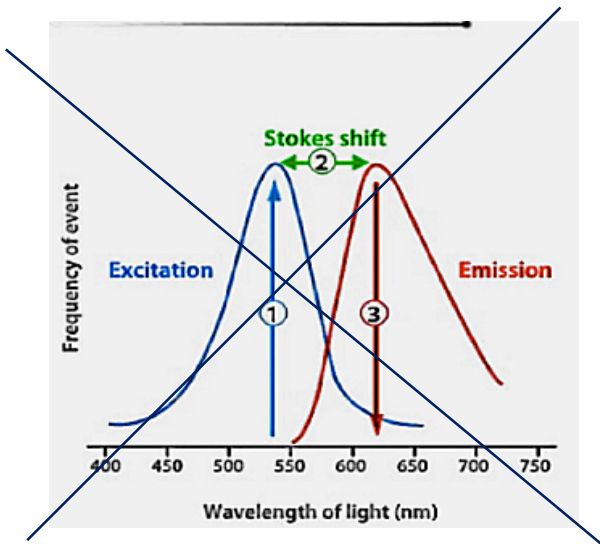
Shuo Chen,<sup>1\*</sup> Adam Z. Weitemier,<sup>1</sup> Xiao Zeng,<sup>2</sup> Linmeng He,<sup>1</sup> Xiyu Wang,<sup>1</sup> Yanqiu Tao,<sup>1</sup> Arthur J. Y. Huang,<sup>1</sup> Yuki Hashimoto-dani,<sup>3</sup> Masanobu Kano,<sup>3,4</sup> Hirohide Iwasaki,<sup>5</sup> Laxmi Kumar Parajuli,<sup>5</sup> Shigeo Okabe,<sup>5</sup> Daniel B. Loong Teh,<sup>6</sup> Angelo H. All,<sup>7</sup> Iku Tsutsui-Kimura,<sup>8</sup> Kenji F. Tanaka,<sup>8</sup> Xiaogang Liu,<sup>2,9\*</sup> Thomas J. McHugh<sup>1,10\*</sup>



# Traditional downconversion: Fluorescent dyes

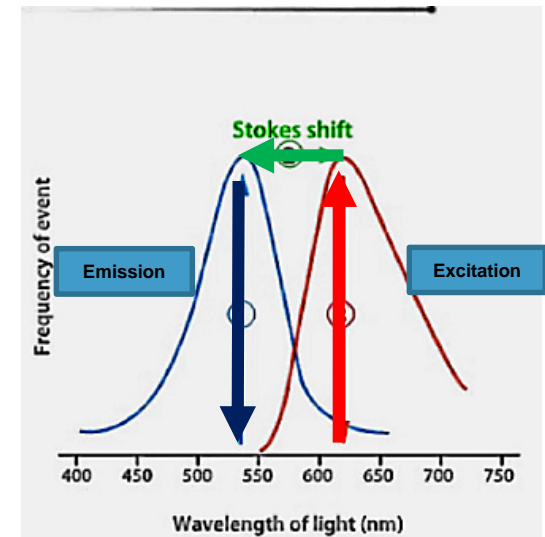
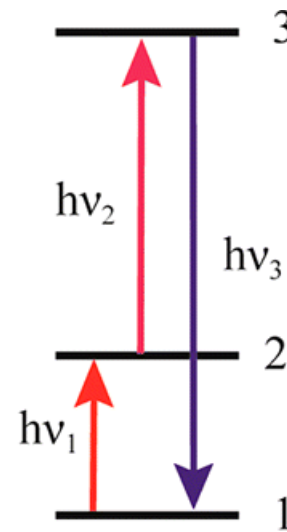
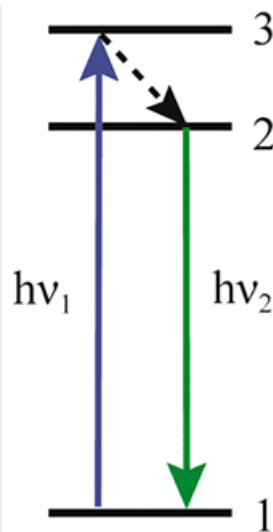
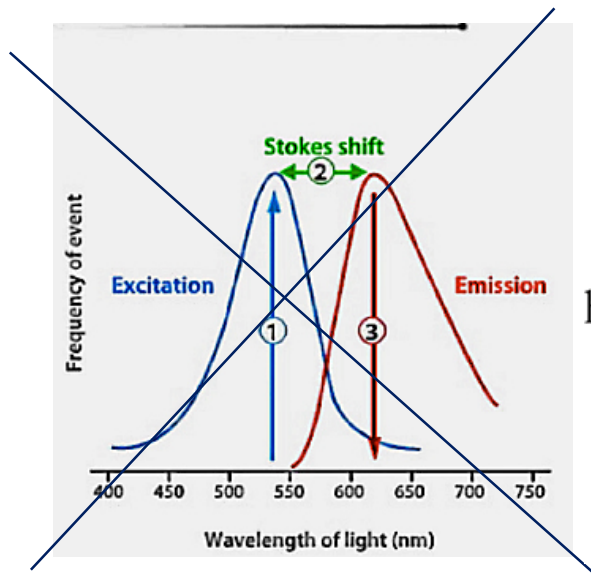


# Photon upconversion (UC)



# Photon upconversion (UC)

- sequential absorption of  $\geq 2$  photons  
→ emission of light at **shorter** wavelength than the excitation wavelength
- anti-Stokes type emission
- E.g infrared light to visible light



# Photon upconversion (UC)

- Organic (polycyclicaromatic hydrocarbons)
- Inorganic: often contain ions of d-block or f-block elements

<div><div>s-Block</div><div>d-Block</div><div>p-Block</div><div>f-Block</div></div>																	
Gruppe																	
1	2											13	14	15	16	17	18
1 H Wasserstoff 1,0079 1	2 He Helium 4,0026 2											5 B Bor 10,811 2/3	6 C Kohlenstoff 12,011 2/4	7 N Stickstoff 14,007 2/5	8 O Sauerstoff 15,999 2/6	9 F Fluor 18,998 2/7	10 Ne Neon 20,180 2/8
3 Li Lithium 6,941 2/1	4 Be Beryllium 9,0122 2/2											13 Al Aluminium 26,982 2/8/3	14 Si Silicium 28,086 2/8/4	15 P Phosphor 30,974 2/8/5	16 S Schwefel 32,065 2/8/6	17 Cl Chlor 35,453 2/8/7	18 Ar Argon 39,948 2/8/8
11 Na Natrium 22,990 2/8/1	12 Mg Magnesium 24,305 2/8/2											31 Ga Gallium 69,723 2/8/18/3	32 Ge Germanium 72,64 2/8/18/4	33 As Arsen 74,922 2/8/18/5	34 Se Selen 78,96 2/8/18/6	35 Br Brom 79,904 2/8/18/7	36 Kr Krypton 83,798 2/8/18/8
19 K Kalium 39,098 2/8/8/1	20 Ca Calcium 40,078 2/8/8/2	21 Sc Scandium 44,956 2/8/9/2	22 Ti Titan 47,867 2/8/10/2	23 V Vanadium 50,942 2/8/11/2	24 Cr Chrom 51,996 2/8/13/1	25 Mn Mangan 54,938 2/8/13/2	26 Fe Eisen 55,845 2/8/14/2	27 Co Cobalt 58,933 2/8/15/2	28 Ni Nickel 58,693 2/8/16/2	29 Cu Kupfer 63,546 2/8/18/1	30 Zn Zink 65,38 2/8/18/2	31 Ga Gallium 69,723 2/8/18/3	32 Ge Germanium 72,64 2/8/18/4	33 As Arsen 74,922 2/8/18/5	34 Se Selen 78,96 2/8/18/6	35 Br Brom 79,904 2/8/18/7	36 Kr Krypton 83,798 2/8/18/8
37 Rb Rubidium 85,468 2/8/18/8/1	38 Sr Strontium 87,62 2/8/18/8/2	39 Y Yttrium 88,906 2/8/18/9/2	40 Zr Zirkon 91,224 2/8/18/10/2	41 Nb Niob 92,906 2/8/18/12/1	42 Mo Molybdän 95,96 2/8/18/13/1	43 Tc Technetium 98,91 2/8/18/13/2	44 Ru Ruthenium 101,07 2/8/18/15/1	45 Rh Rhodium 102,91 2/8/18/16/1	46 Pd Palladium 106,42 2/8/18/18	47 Ag Silber 107,87 2/8/18/18/1	48 Cd Cadmium 112,41 2/8/18/18/2	49 In Indium 114,82 2/8/18/18/3	50 Sn Zinn 118,71 2/8/18/18/4	51 Sb Antimon 121,76 2/8/18/18/5	52 Te Tellur 127,60 2/8/18/18/6	53 I Jod 126,90 2/8/18/18/7	54 Xe Xenon 131,29 2/8/18/18/8
55 Cs Cäsium 132,91 2/8/18/18/8/1	56 Ba Barium 137,33 2/8/18/18/8/2	57-71 siehe unten	72 Hf Hafnium 178,49 2/8/18/32/10/2	73 Ta Tantal 180,95 2/8/18/32/11/2	74 W Wolfram 183,84 2/8/18/32/12/2	75 Re Rhenium 186,21 2/8/18/32/13/2	76 Os Osmium 190,23 2/8/18/32/14/2	77 Ir Iridium 192,22 2/8/18/32/15/2	78 Pt Platin 195,08 2/8/18/32/17/1	79 Au Gold 196,97 2/8/18/32/18/1	80 Hg Quecksilber 200,59 2/8/18/32/18/2	81 Tl Thallium 204,38 2/8/18/32/18/3	82 Pb Blei 207,2 2/8/18/32/18/4	83 Bi Bismut 208,98 2/8/18/32/18/5	84 Po Polonium 209,98 2/8/18/32/18/6	85 At Astat (210) 2/8/18/32/18/7	86 Rn Radon (222) 2/8/18/32/18/8
87 Fr Francium (223) 2/8/18/32/18/8/1	88 Ra Radium 226,03 2/8/18/32/18/8/2	89-103 siehe unten	104 Rf Rutherfordium (261) 2/8/18/32/32/10/2	105 Db Dubnium (262) 2/8/18/32/32/11/2	106 Sg Seaborgium (263) 2/8/18/32/32/12/2	107 Bh Bohrium (262) 2/8/18/32/32/13/2	108 Hs Hassium (265) 2/8/18/32/32/14/2	109 Mt Meitnerium (266) 2/8/18/32/32/15/2	110 Ds Darmstadtium (269) 2/8/18/32/32/17/1	111 Rg Röntgenium (272) 2/8/18/32/32/18/1	112 Cn Copernicium (277) 2/8/18/32/32/18/2	113 Uut Ununtrium (287) 2/8/18/32/32/18/3	114 Uuq Ununquadium (289) 2/8/18/32/32/18/4	115 Uup Ununpentium (288) 2/8/18/32/32/18/5	116 Uuh Ununhexium (289) 2/8/18/32/32/18/6	117 Uus Ununseptium (293) 2/8/18/32/32/18/7	118 Uuo Ununoctium (294) 2/8/18/32/32/18/8
↓																	
Lanthanoide																	
57 La Lanthan 138,91 2/8/18/18/9/2	58 Ce Cer 140,12 2/8/18/19/9/2	59 Pr Praseodym 140,91 2/8/18/21/9/2	60 Nd Neodym 144,24 2/8/18/22/9/2	61 Pm Promethium 146,90 2/8/18/23/9/2	62 Sm Samarium 150,36 2/8/18/24/9/2	63 Eu Europium 151,96 2/8/18/25/9/2	64 Gd Gadolinium 157,25 2/8/18/25/9/2	65 Tb Terbium 158,93 2/8/18/27/9/2	66 Dy Dysprosium 162,50 2/8/18/28/9/2	67 Ho Holmium 164,93 2/8/18/29/9/2	68 Er Erbium 167,26 2/8/18/30/9/2	69 Tm Thulium 168,93 2/8/18/31/9/2	70 Yb Ytterbium 173,05 2/8/18/32/9/2	71 Lu Lutetium 174,97 2/8/18/32/9/2			
Actinoide																	
89 Ac Actinium (227) 2/8/18/32/18/9/2	90 Th Thorium 232,04 2/8/18/32/18/10/2	91 Pa Protaktinium 231,04 2/8/18/32/21/9/2	92 U Uran 238,03 2/8/18/32/21/9/2	93 Np Neptunium 237,05 2/8/18/32/22/9/2	94 Pu Plutonium (244,10) 2/8/18/32/24/9/2	95 Am Americium (243,10) 2/8/18/32/25/9/2	96 Cm Curium (247,10) 2/8/18/32/25/10/2	97 Bk Berkelium (247,10) 2/8/18/32/25/10/2	98 Cf Californium (251,10) 2/8/18/32/28/8/2	99 Es Einsteinium (254,10) 2/8/18/32/29/8/2	100 Fm Fermium (257,10) 2/8/18/32/30/8/2	101 Md Mendelevium (258) 2/8/18/32/31/8/2	102 No Nobelium (259) 2/8/18/32/32/8/2	103 Lr Lawrencium (260) 2/8/18/32/32/8/2			



# Photon upconversion (UC)

- Organic (polycyclicaromatic hydrocarbons)
- Inorganic: often contain ions of d-block or f-block elements

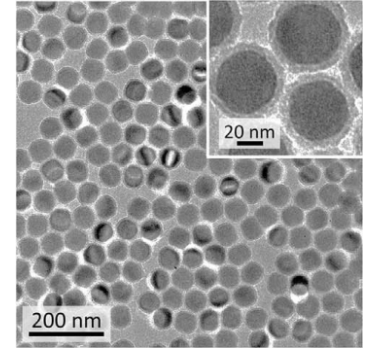
s-Block
d-Block  
p-Block
f-Block

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1 1 H Wasserstoff 1,0079 1	2 4 He Helium 4,0026 2																
3 3 Li Lithium 6,941 2/1	4 4 Be Beryllium 9,0122 2/2											5 5 B Bor 10,811 2/3	6 6 C Kohlenstoff 12,011 2/4	7 7 N Stickstoff 14,007 2/5	8 8 O Sauerstoff 15,999 2/6	9 9 F Fluor 18,998 2/7	10 10 Ne Neon 20,180 2/8
11 11 Na Natrium 22,990 2/8/1	12 12 Mg Magnesium 24,305 2/8/2											13 13 Al Aluminium 26,982 2/8/3	14 14 Si Silicium 28,086 2/8/4	15 15 P Phosphor 30,974 2/8/5	16 16 S Schwefel 32,065 2/8/6	17 17 Cl Chlor 35,453 2/8/7	18 18 Ar Argon 39,948 2/8/8
19 19 K Kalium 39,098 2/8/8/1	20 20 Ca Calcium 40,078 2/8/8/2	21 21 Sc Scandium 44,956 2/8/18/9/2	22 22 Ti Titan 47,867 2/8/18/10/2	23 23 V Vanadium 50,942 2/8/11/2	24 24 Cr Chrom 51,996 2/8/13/1	25 25 Mn Mangan 54,938 2/8/13/2	26 26 Fe Eisen 55,845 2/8/14/2	27 27 Co Cobalt 58,933 2/8/15/2	28 28 Ni Nickel 58,693 2/8/16/2	29 29 Cu Kupfer 63,546 2/8/18/1	30 30 Zn Zink 65,38 2/8/18/2	31 31 Ga Gallium 69,723 2/8/18/3	32 32 Ge Germanium 72,64 2/8/18/4	33 33 As Arsen 74,922 2/8/18/5	34 34 Se Selen 78,96 2/8/18/6	35 35 Br Brom 79,904 2/8/18/7	36 36 Kr Krypton 83,798 2/8/18/8
39 39 Y Yttrium 88,906 2/8/18/9/2	40 40 Zr Zirkon 91,224 2/8/18/10/2	41 41 Nb Niob 92,906 2/8/18/12/1	42 42 Mo Molybdän 95,96 2/8/18/13/1	43 43 Tc Technetium 98,91 2/8/18/13/2	44 44 Ru Ruthenium 101,07 2/8/18/15/1	45 45 Rh Rhodium 102,91 2/8/18/16/1	46 46 Pd Palladium 106,42 2/8/18/18	47 47 Ag Silber 107,87 2/8/18/18/1	48 48 Cd Cadmium 112,41 2/8/18/18/2	49 49 In Indium 114,82 2/8/18/18/2	50 50 Sn Zinn 118,71 2/8/18/18/2	51 51 Sb Antimon 121,76 2/8/18/18/3	52 52 Te Tellur 127,60 2/8/18/18/4	53 53 I Jod 126,91 2/8/18/18/5	54 54 Xe Xenon 131,29 2/8/18/18/6	55 55 Ba Baryum 137,33 2/8/18/18/7	56 56 La Lanthan 138,91 2/8/18/18/9/2
57-71 siehe unten	72 72 Hf Hafnium 178,49 2/8/18/32/10/2	73 73 Ta Tantal 180,95 2/8/18/32/11/2	74 74 W Wolfram 183,84 2/8/18/32/12/2	75 75 Re Rhenium 186,21 2/8/18/32/13/2	76 76 Os Osmium 190,23 2/8/18/32/14/2	77 77 Ir Iridium 192,22 2/8/18/32/15/2	78 78 Pt Platin 195,08 2/8/18/32/17/1	79 79 Au Gold 196,97 2/8/18/32/18/1	80 80 Hg Quecksilber 200,59 2/8/18/32/18/2	81 81 Tl Thallium 204,38 2/8/18/32/18/2	82 82 Pb Blei 207,2 2/8/18/32/18/2	83 83 Bi Bismut 208,98 2/8/18/32/18/3	84 84 Po Polonium 209 2/8/18/32/18/4	85 85 At Astatin 210 2/8/18/32/18/5	86 86 Rn Radon 222 2/8/18/32/18/6	87 87 Fr Francium 223 2/8/18/32/18/7	88-103 siehe unten
57 57 La Lanthan 138,91 2/8/18/18/9/2	58 58 Ce Cer 140,12 2/8/18/19/9/2	59 59 Pr Praseodym 140,91 2/8/18/21/9/2	60 60 Nd Neodym 144,24 2/8/18/22/9/2	61 61 Pm Promethium 144,91 2/8/18/23/9/2	62 62 Sm Samarium 150,36 2/8/18/24/9/2	63 63 Eu Europium 151,96 2/8/18/25/9/2	64 64 Gd Gadolinium 157,25 2/8/18/25/9/2	65 65 Tb Terbium 158,93 2/8/18/27/9/2	66 66 Dy Dysprosium 162,50 2/8/18/28/9/2	67 67 Ho Holmium 164,93 2/8/18/29/9/2	68 68 Er Erbium 167,26 2/8/18/30/9/2	69 69 Tm Thulium 168,93 2/8/18/31/9/2	70 70 Yb Ytterbium 173,05 2/8/18/32/9/2	71 71 Lu Lutetium 174,97 2/8/18/32/9/2	72 72 Hf Hafnium 178,49 2/8/18/32/10/2	73 73 Ta Tantal 180,95 2/8/18/32/11/2	74 74 W Wolfram 183,84 2/8/18/32/12/2
89 89 Ac Actinium 227 2/8/18/32/18/9/2	90 90 Th Thorium 232,04 2/8/18/32/18/10/2	91 91 Pa Protaktinium 231,04 2/8/18/32/21/9/2	92 92 U Uran 238,03 2/8/18/32/21/9/2	93 93 Np Neptunium 237,05 2/8/18/32/22/9/2	94 94 Pu Plutonium 244,10 2/8/18/32/24/8/2	95 95 Am Americium 243,10 2/8/18/32/25/8/2	96 96 Cm Curium 247,10 2/8/18/32/25/10/2	97 97 Bk Berkelium 247,10 2/8/18/32/25/10/2	98 98 Cf Californium 251,10 2/8/18/32/28/8/2	99 99 Es Einsteinium 254,10 2/8/18/32/29/8/2	100 100 Fm Fermium 257,10 2/8/18/32/30/8/2	101 101 Md Mendelevium 258 2/8/18/32/31/8/2	102 102 No Nobelium 259 2/8/18/32/32/8/2	103 103 Lr Lawrencium 260 2/8/18/32/32/8/2	104 104 Rf Rutherfordium 261 2/8/18/32/32/10/2	105 105 Db Dubnium 262 2/8/18/32/32/11/2	106 106 Sg Seaborgium 263 2/8/18/32/32/12/2

# Photon upconversion (UC)

- Inorganic:

- NaYF<sub>4</sub> = popular host for lanthanide UCNPs  
Sodium yttrium fluoride (1:1:4)
- Dopant ions Er<sup>3+</sup>, Tm<sup>3+</sup> = activators (<2 mol %)
- Yb<sup>3+</sup> is often codoped as a sensitizer to enhance upconversion emission

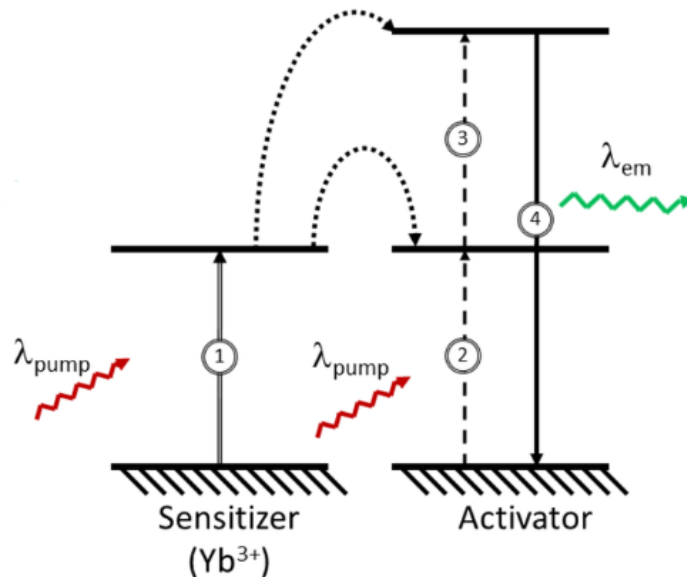


Shuo Chen, 2018, Science

Jing Zhou, 2015 Chem. Rev.

<b>39</b>	<b>Y</b>
Yttrium	
88,906	
2/8/18/9/2	

Host



<b>68</b>	<b>Er</b>	<b>69</b>	<b>Tm</b>	<b>70</b>	<b>Yb</b>
Erbium		Thulium		Ytterbium	
167,26		168,93		173,05	
2/8/18/30/8/2		2/8/18/31/8/2		2/8/18/32/8/2	

Activators

Sensitizer



# Photon upconversion (UC)

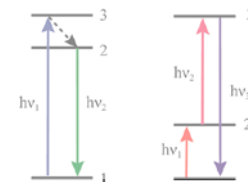
CHEMICAL  
REVIEWS

Review

pubs.acs.org/CR

Upconversion Luminescent Materials: Advances and Applications

Jing Zhou,<sup>†</sup> Qian Liu,<sup>†</sup> Wei Feng, Yun Sun, and Fuyou Li\*

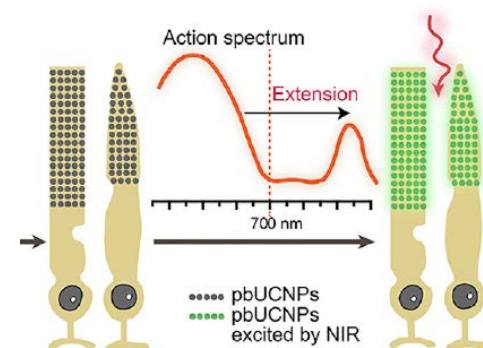


## Article

### Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae

Yuqian Ma,<sup>1,5</sup> Jin Bao,<sup>1,2,5,\*</sup> Yuanwei Zhang,<sup>3,5</sup> Zhanjun Li,<sup>3</sup> Xiangyu Zhou,<sup>1</sup> Changlin Wan,<sup>1</sup> Ling Huang,<sup>3</sup> Yang Zhao,<sup>3</sup> Gang Han,<sup>3,\*</sup> and Tian Xue<sup>1,2,4,6,\*</sup>

Cell



## NEUROSCIENCE

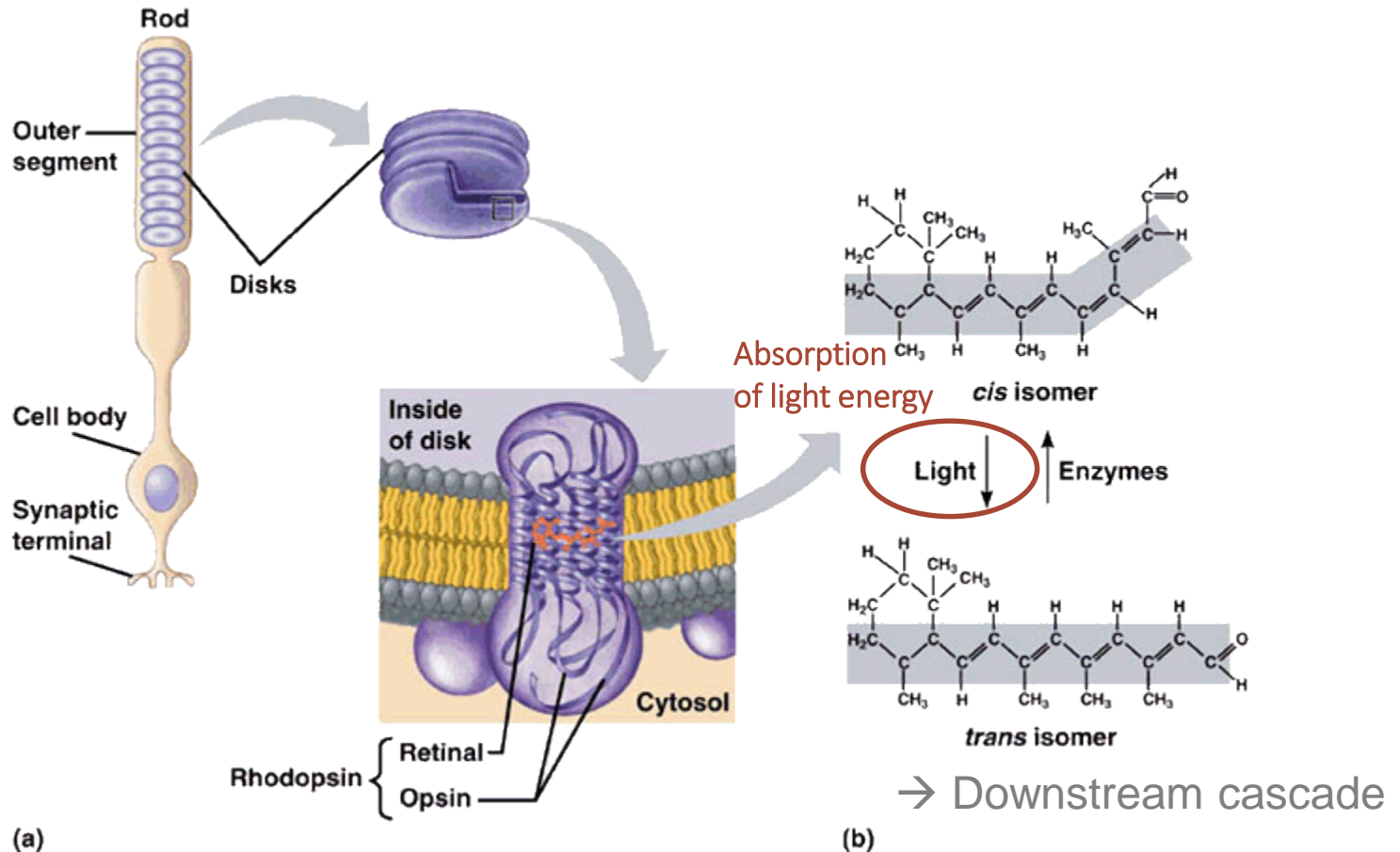
### Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics

Shuo Chen,<sup>1\*</sup> Adam Z. Weitemier,<sup>1</sup> Xiao Zeng,<sup>2</sup> Linmeng He,<sup>1</sup> Xiyu Wang,<sup>1</sup> Yanqiu Tao,<sup>1</sup> Arthur J. Y. Huang,<sup>1</sup> Yuki Hashimoto-dani,<sup>3</sup> Masanobu Kano,<sup>3,4</sup> Hirohide Iwasaki,<sup>5</sup> Laxmi Kumar Parajuli,<sup>5</sup> Shigeo Okabe,<sup>5</sup> Daniel B. Loong Teh,<sup>6</sup> Angelo H. All,<sup>7</sup> Iku Tsutsui-Kimura,<sup>8</sup> Kenji F. Tanaka,<sup>8</sup> Xiaogang Liu,<sup>2,9\*</sup> Thomas J. McHugh<sup>1,10\*</sup>



# Near-Infrared Vision

- Opsins would have to be very sensitive to **low energy**

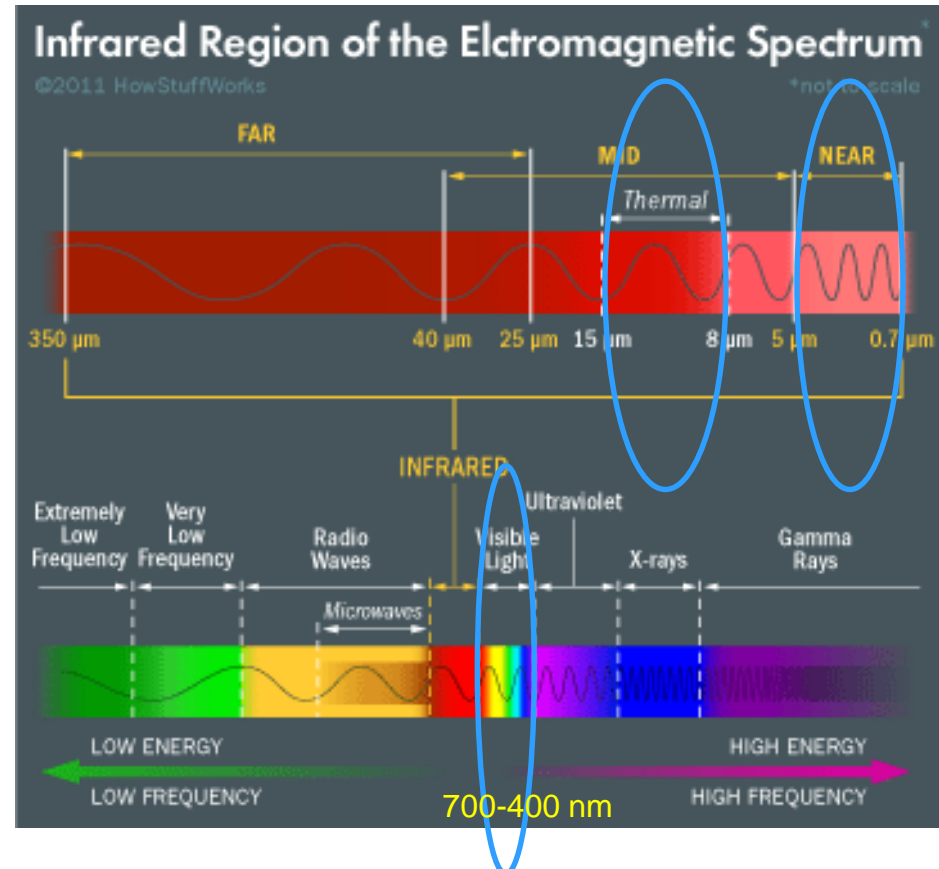


# Near-Infrared Vision

- Opsins would have to be very sensitive to low energy → thermal noise

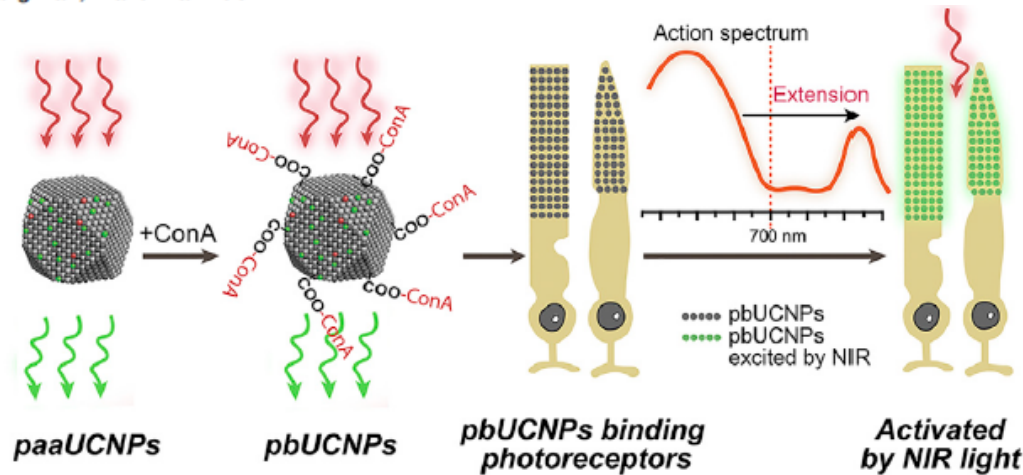
→ Dong-Gen Luo, 2011 Science

- Alternative:  
Conversion to  
higher energy signal  
via **photoreceptor-**  
**binding upconversion**  
**nanoparticles**  
(pbUCNPs)



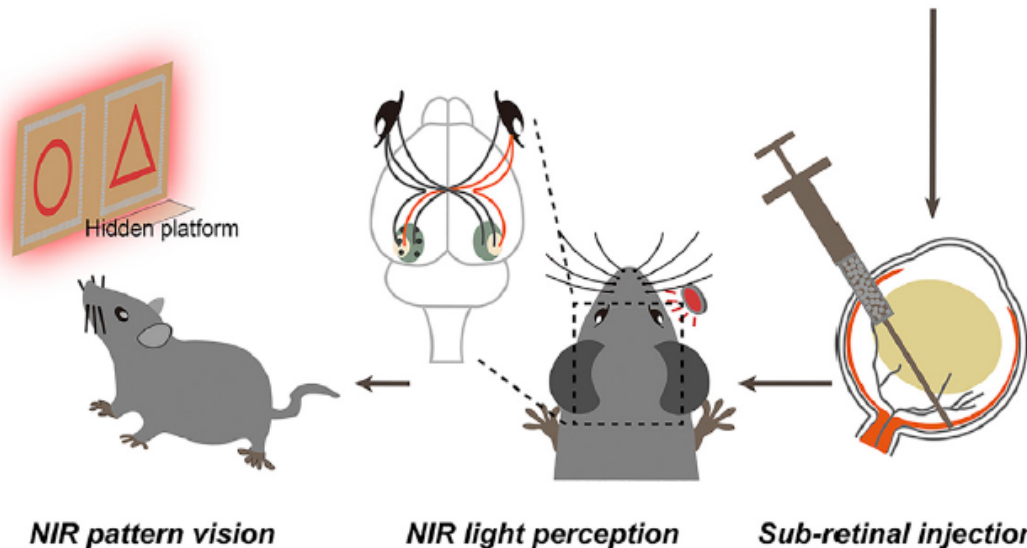
# Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae

Yuqian Ma,<sup>1,5</sup> Jin Bao,<sup>1,2,5,\*</sup> Yuanwei Zhang,<sup>3,5</sup> Zhanjun Li,<sup>3</sup> Xiangyu Zhou,<sup>1</sup> Changlin Wan,<sup>1</sup> Ling Huang,<sup>3</sup> Yang Zhao,<sup>3</sup> Gang Han,<sup>3,\*</sup> and Tian Xue<sup>1,2,4,5,\*</sup>



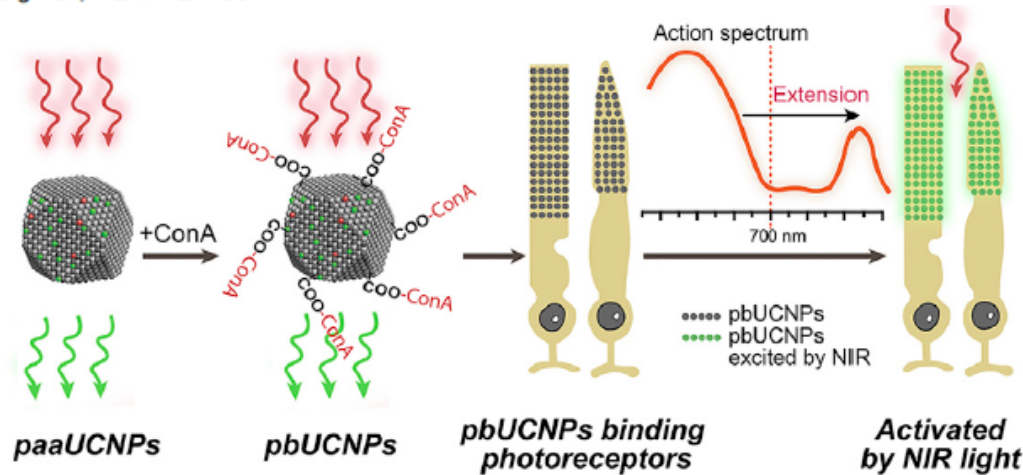
photoreceptor-binding upconversion nanoparticles (pbUCNPs)

- Self-powered
- Biocompatible
- Injectable



# Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae

Yuqian Ma,<sup>1,5</sup> Jin Bao,<sup>1,2,5,\*</sup> Yuanwei Zhang,<sup>3,5</sup> Zhanjun Li,<sup>3</sup> Xiangyu Zhou,<sup>1</sup> Changlin Wan,<sup>1</sup> Ling Huang,<sup>3</sup> Yang Zhao,<sup>3</sup> Gang Han,<sup>3,\*</sup> and Tian Xue<sup>1,2,4,6,\*</sup>

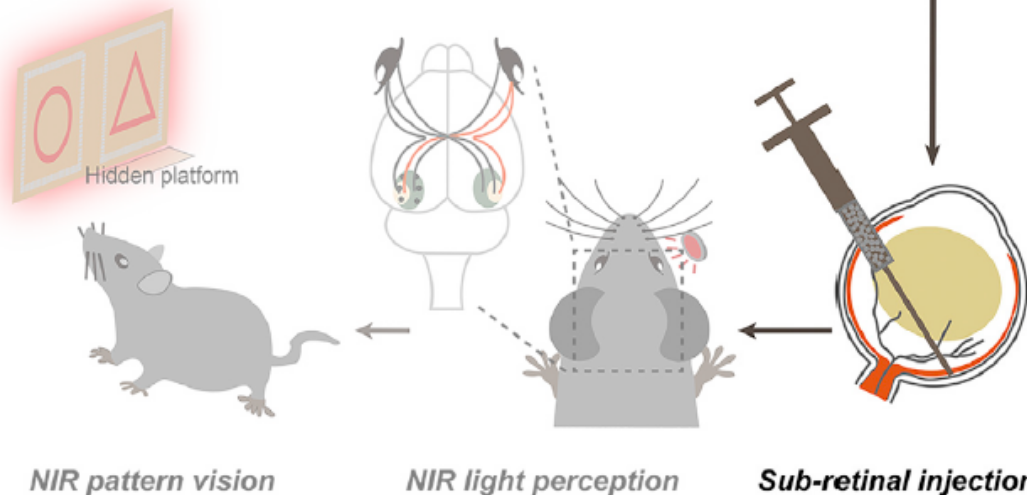


photoreceptor-binding upconversion nanoparticles (pbUCNPs)

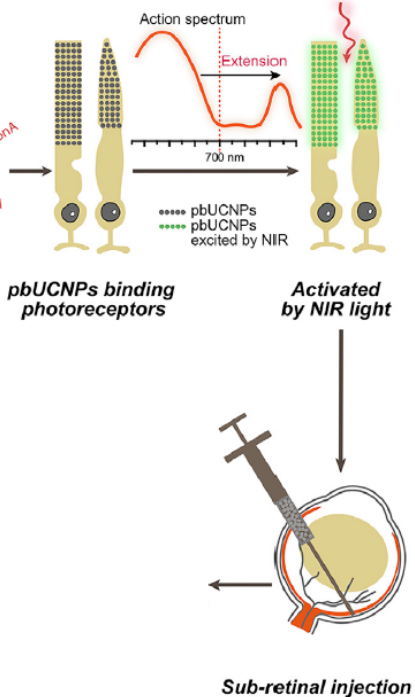
- Self-powered
- Biocompatible
- Injectable

poly acrylic acid coated UCNPs (paaUCNP) + concanavalin A protein (ConA)

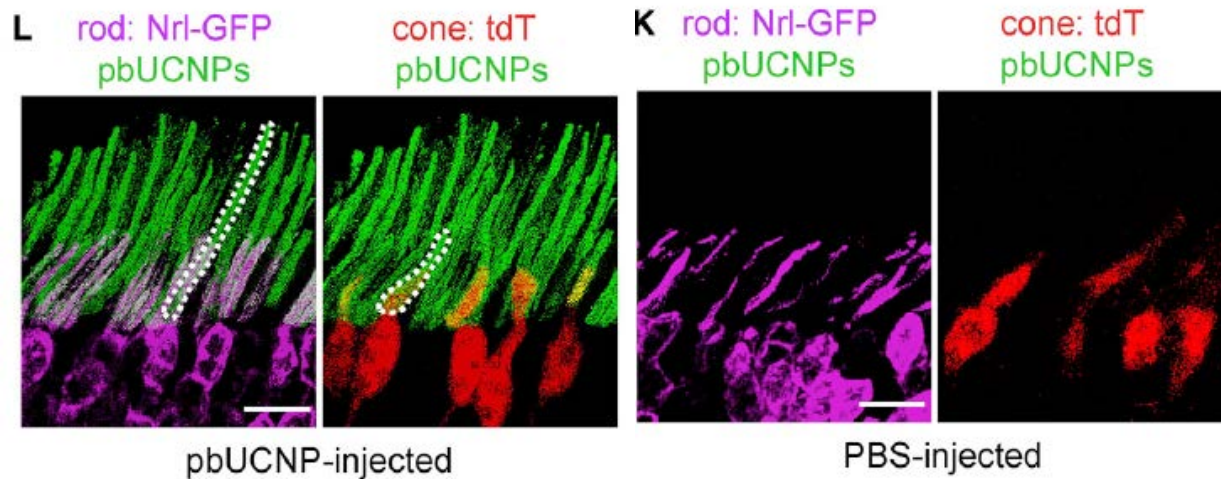
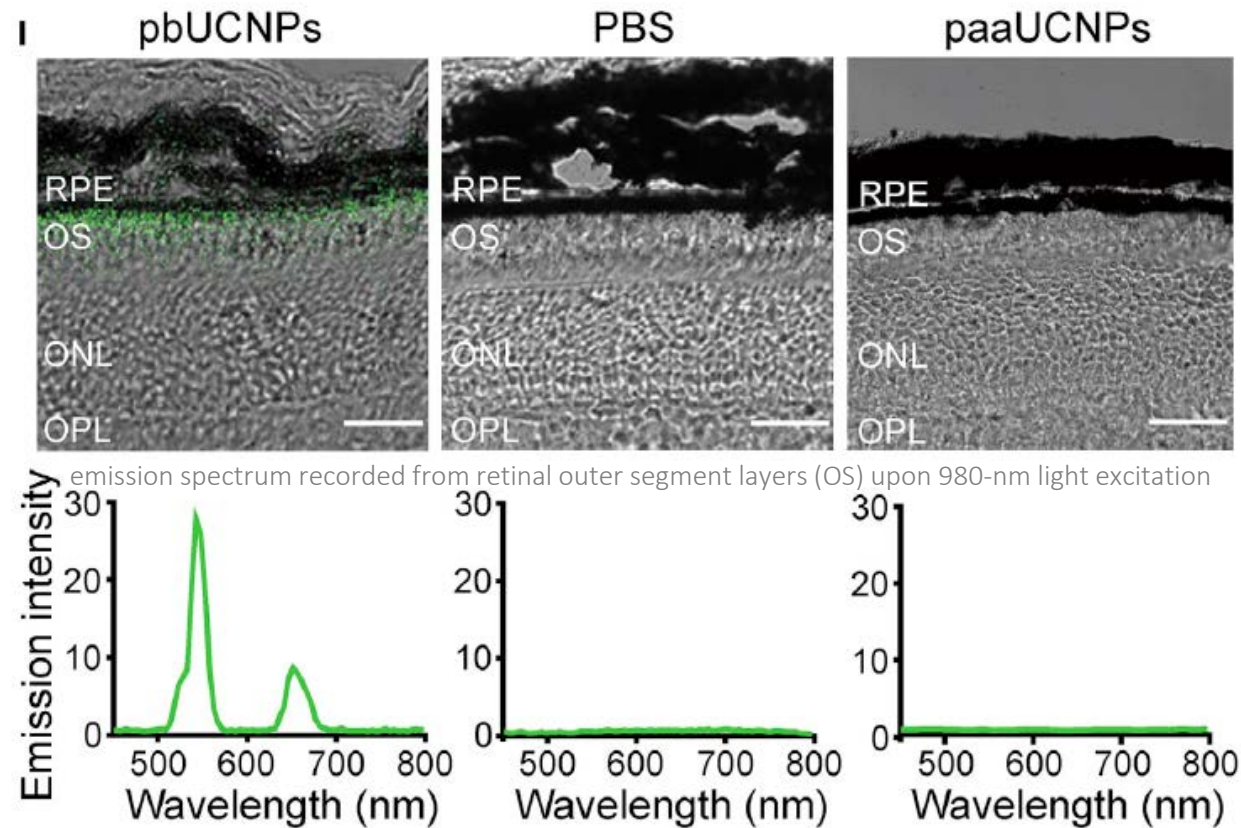
→ glycosidic bonds with sugar residues on OS of photo receptors







overlays of transmission and luminescence optical images (green: 980-nm ex/535-nm em) of retinal slices

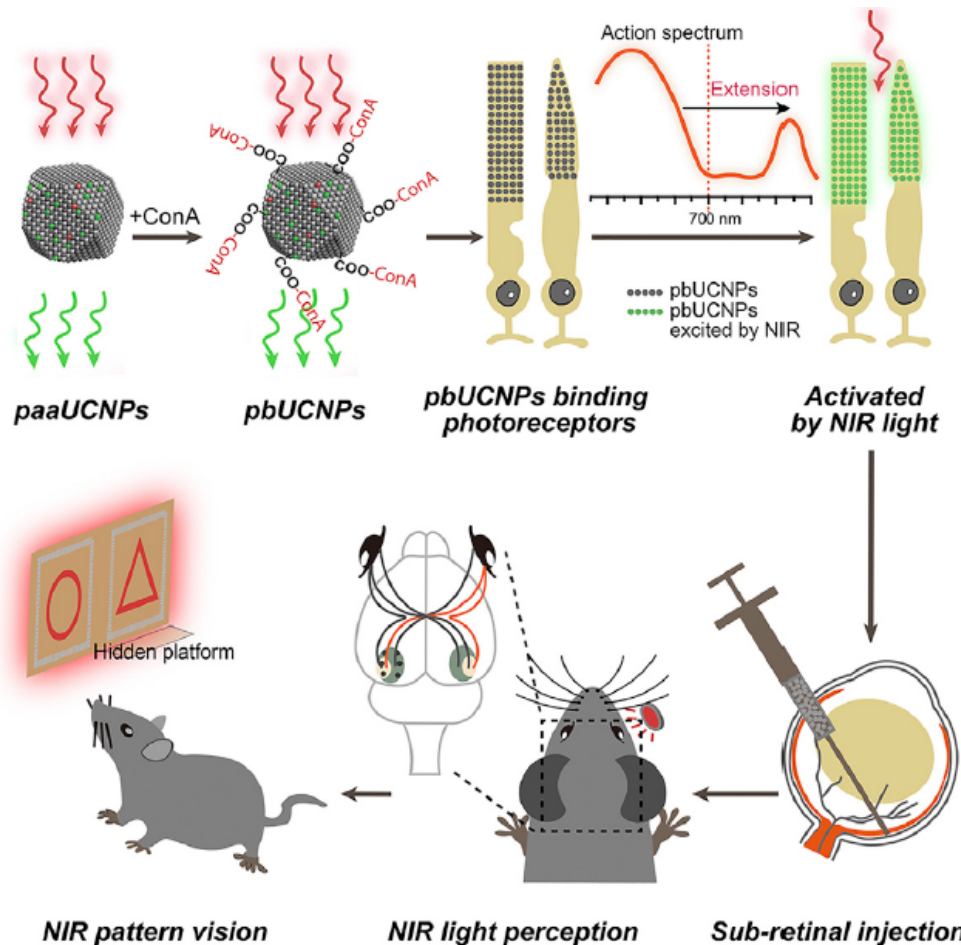


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photoreceptor-binding upconversion  
nanoparticles (pbUCNPs)

- Self-powered
- **Biocompatible**
- Injectable

Side effects e.g. cataracts, corneal opacity

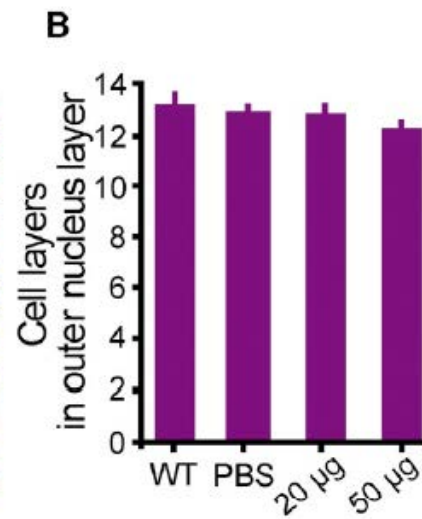
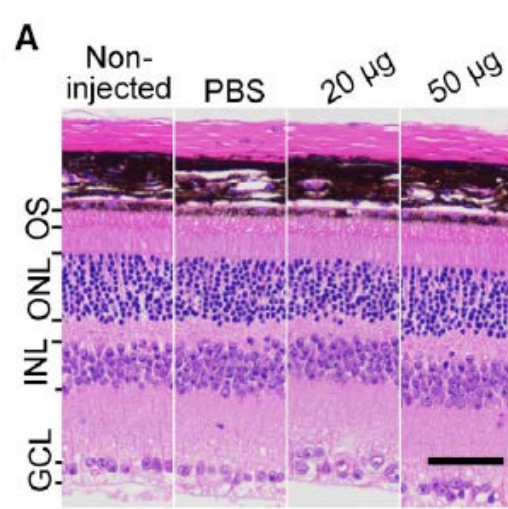
Only minor, transient (2 weeks)

Comparable to any sub-retinal injection

X retinal degeneration

X inflammation (Iba1 stain)

X apoptosis (TUNEL stain)



photoreceptor-binding upconversion nanoparticles (pbUCNPs)

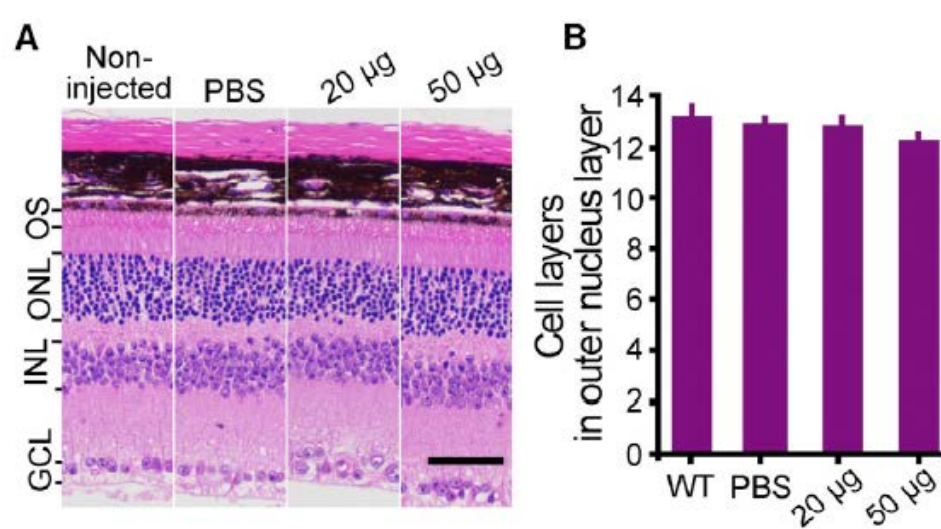
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**X retinal degeneration**

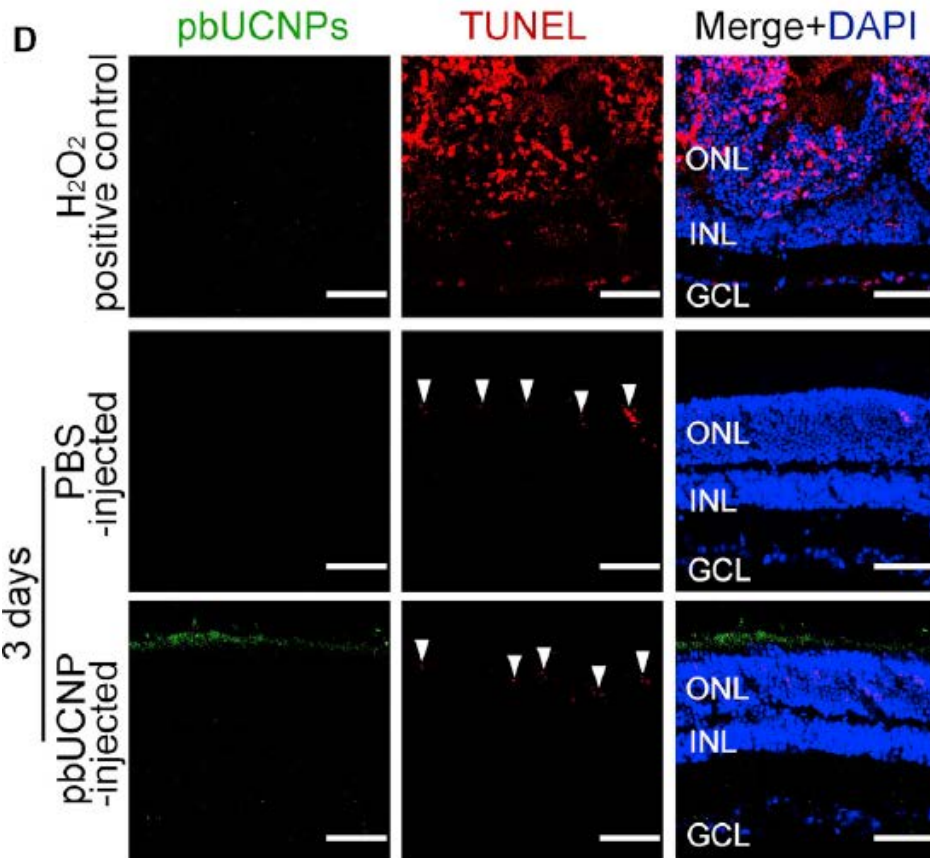
**X inflammation** (Iba1 stain)

**X apoptosis** (TUNEL stain)



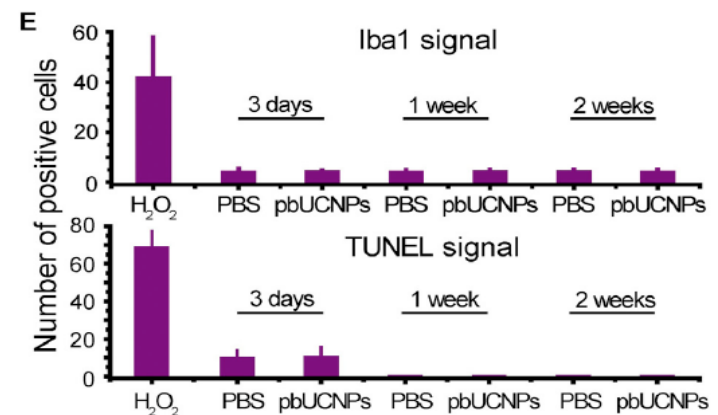
photoreceptor-binding upconversion nanoparticles (pbUCNPs)

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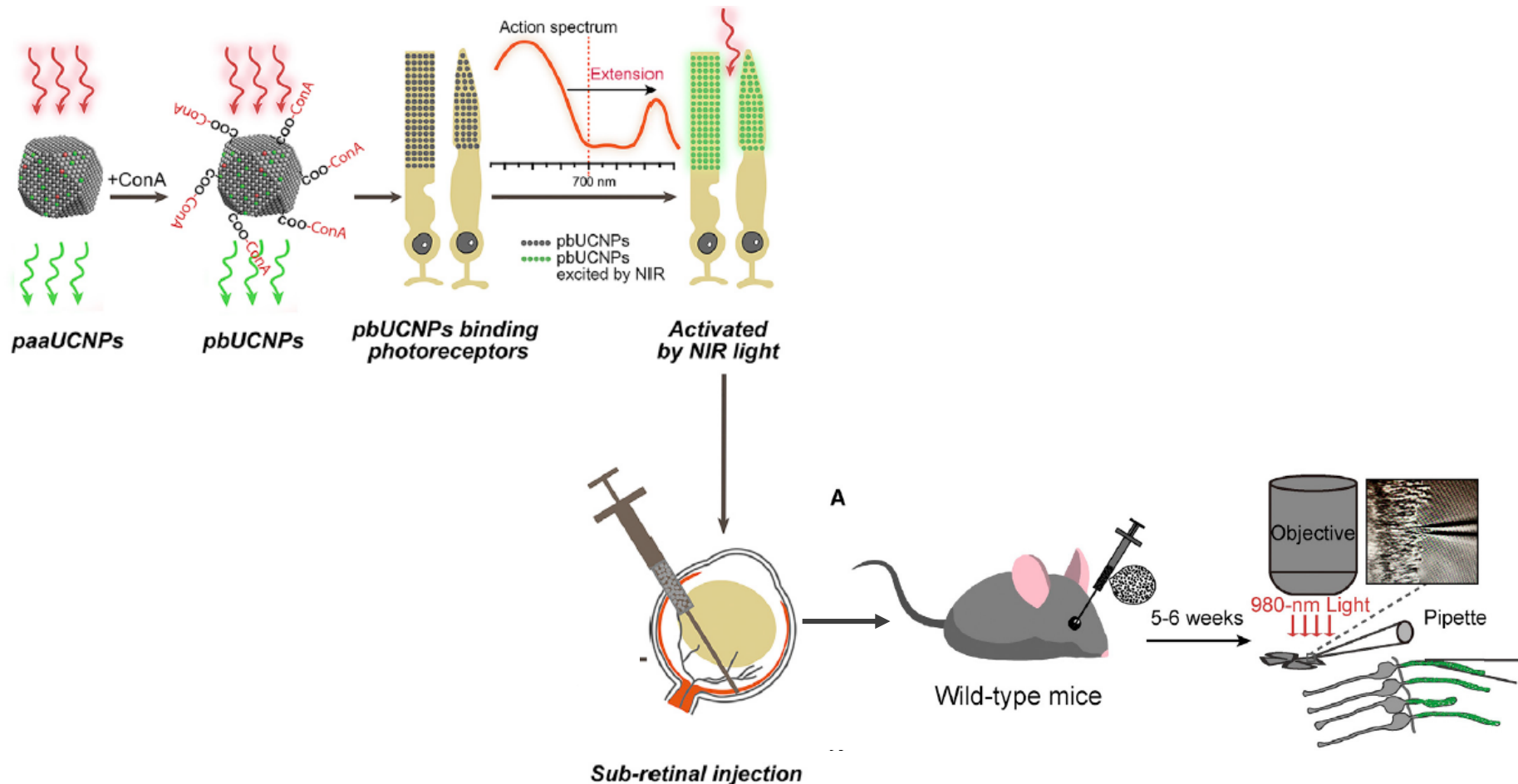
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# photoreceptor-binding upconversion nanoparticles (pbUCNPs)

## → Assessment of Photoreceptor Activation:

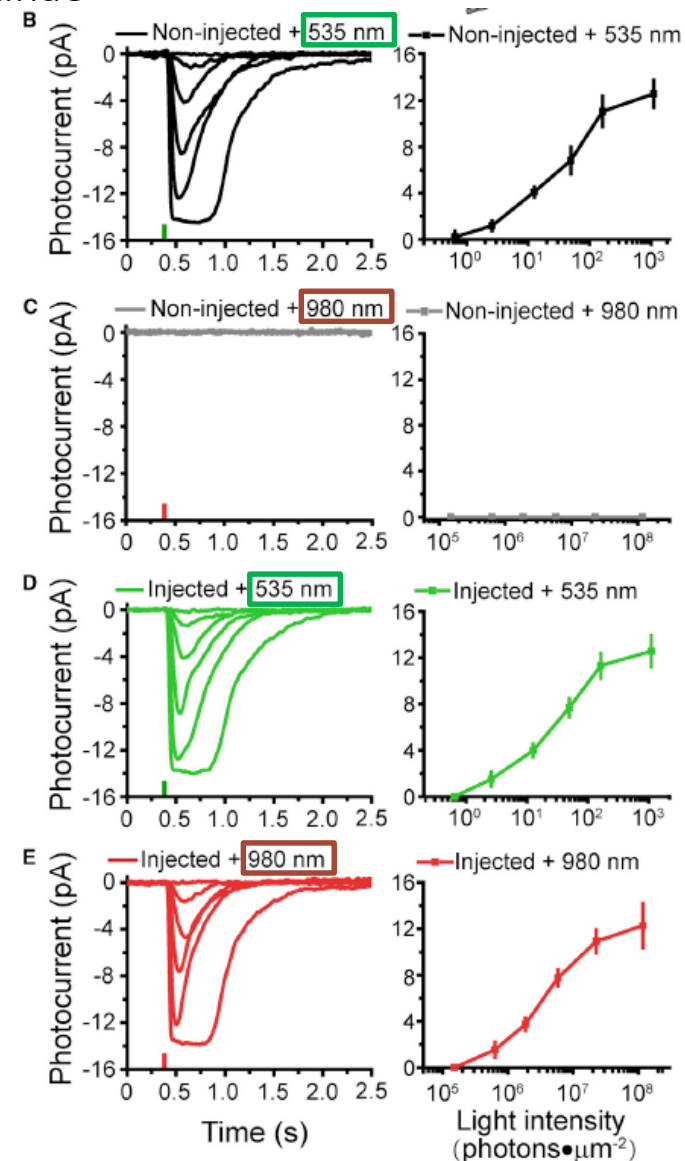
- Single rod pipette recordings on acutely dissected retinæ
- Population response *in vivo* in ERG



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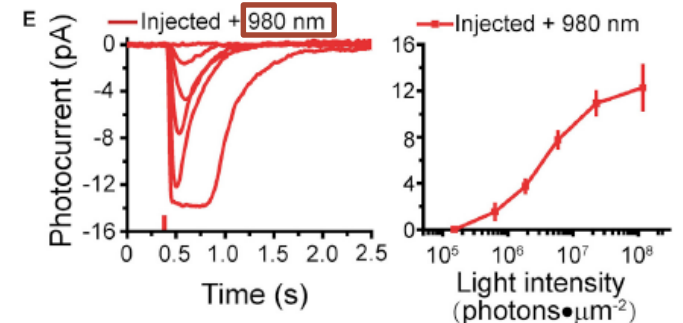
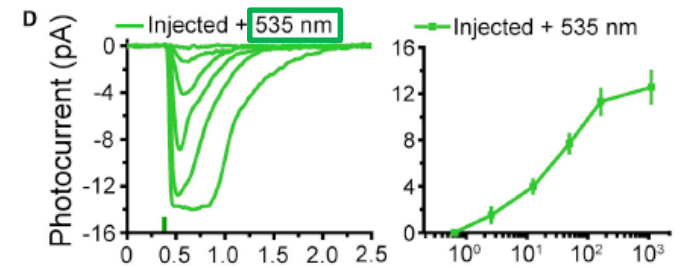
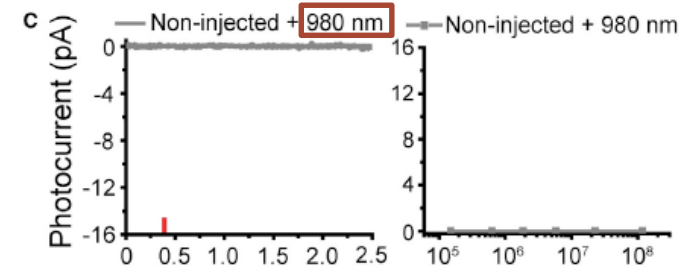
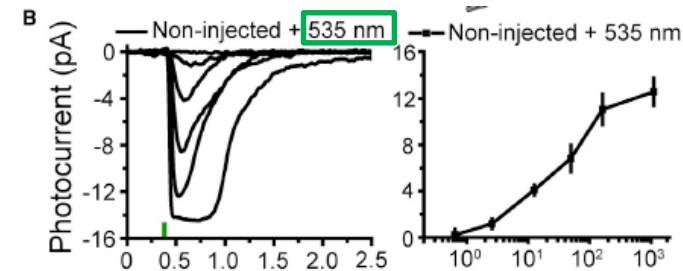
- Single rod pipette recordings on acutely dissected retinæ
  - Amplitude and kinetics of photocurrents elicited by **NIR** vs **VL** were identical
  - No delay in response to **NIR** compared to **VL**
  - No alteration of light adaptation



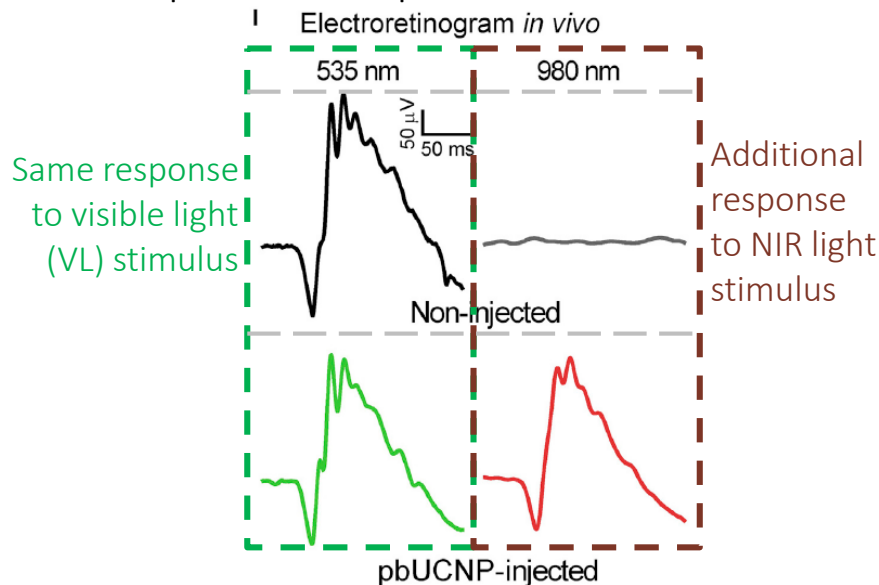
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- Population response *in vivo* in ERG

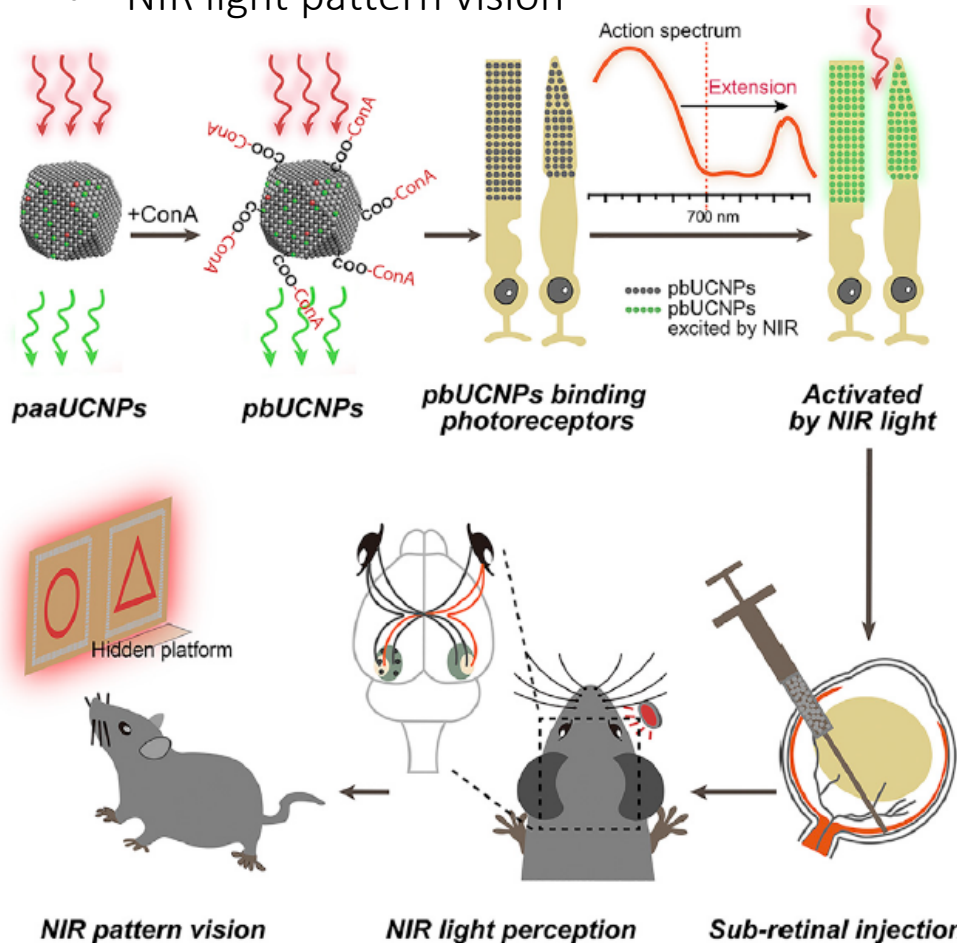




# photoreceptor-binding upconversion nanoparticles (pbUCNPs)

## → Assessment of **Light Sensation** in the Mice:

- Pupillary light reflexes upon NIR light stimulus → sub-conscious sensation
- Light-dark box experiments → conscious sensation
- Light-induced fear conditioning
- Recording visually evoked potentials (VEPs) in visual cortex
- NIR light pattern vision

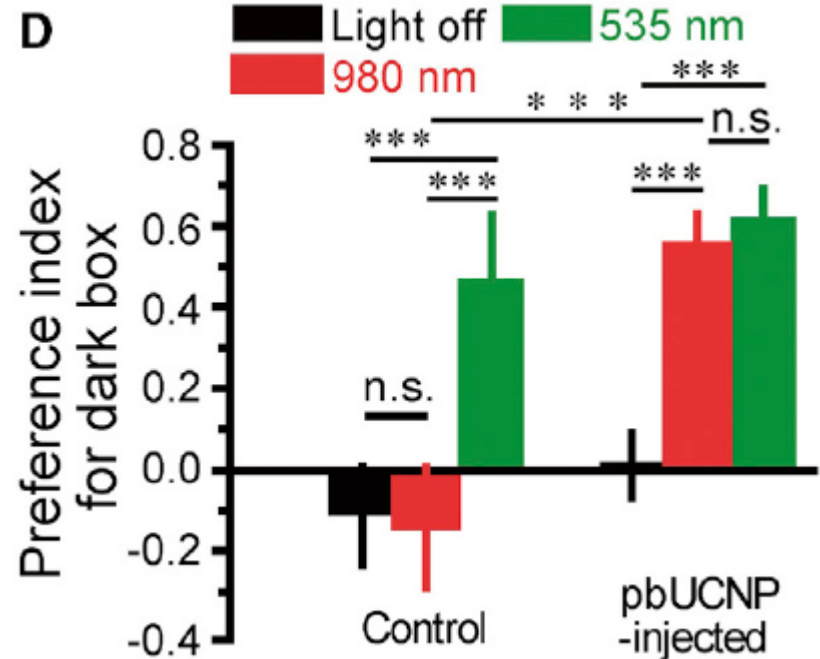
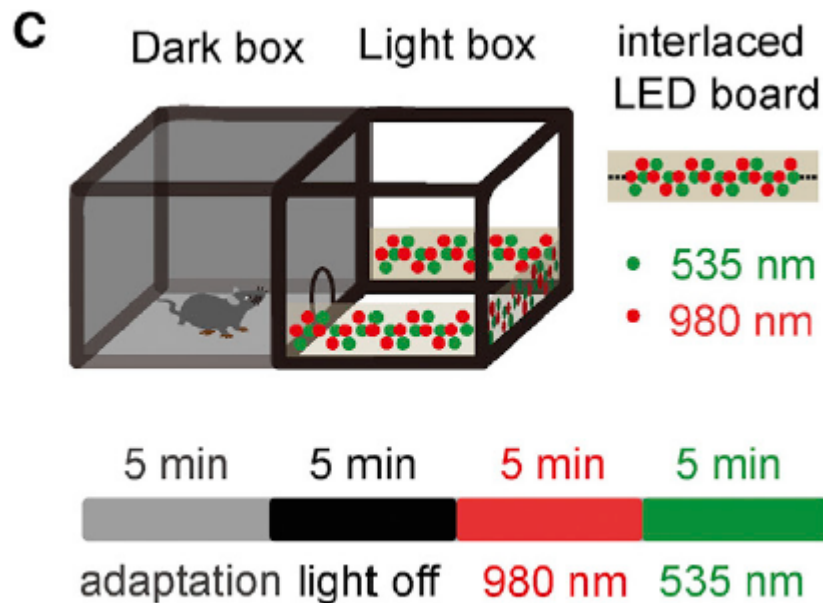




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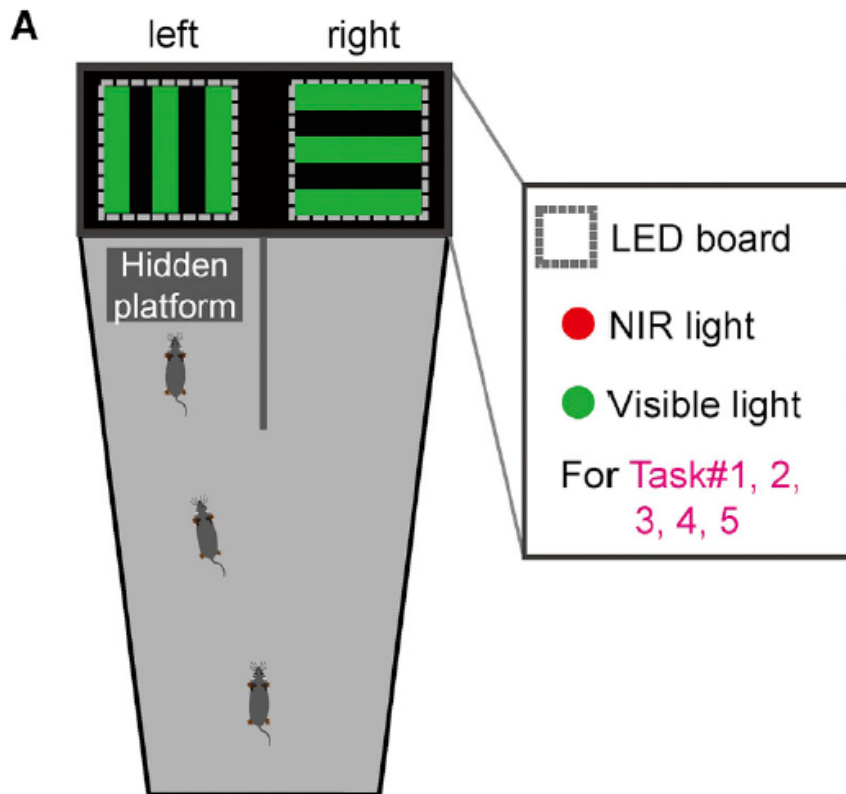


- All mice prefer dark box over VL illuminated box
- pbUCNP injected mice chose dark box over NIR illuminated box
- Control mice had no preference in dark vs NIR illumination

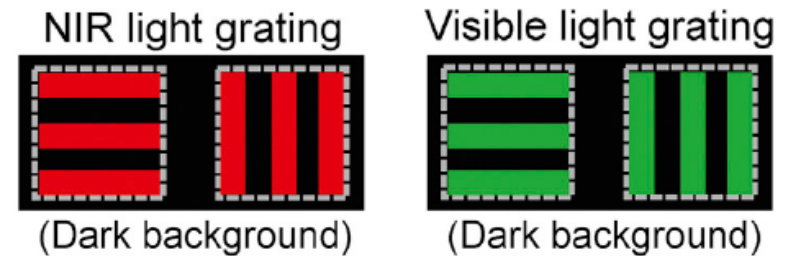
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- **NIR light pattern vision**



## **Task#1**

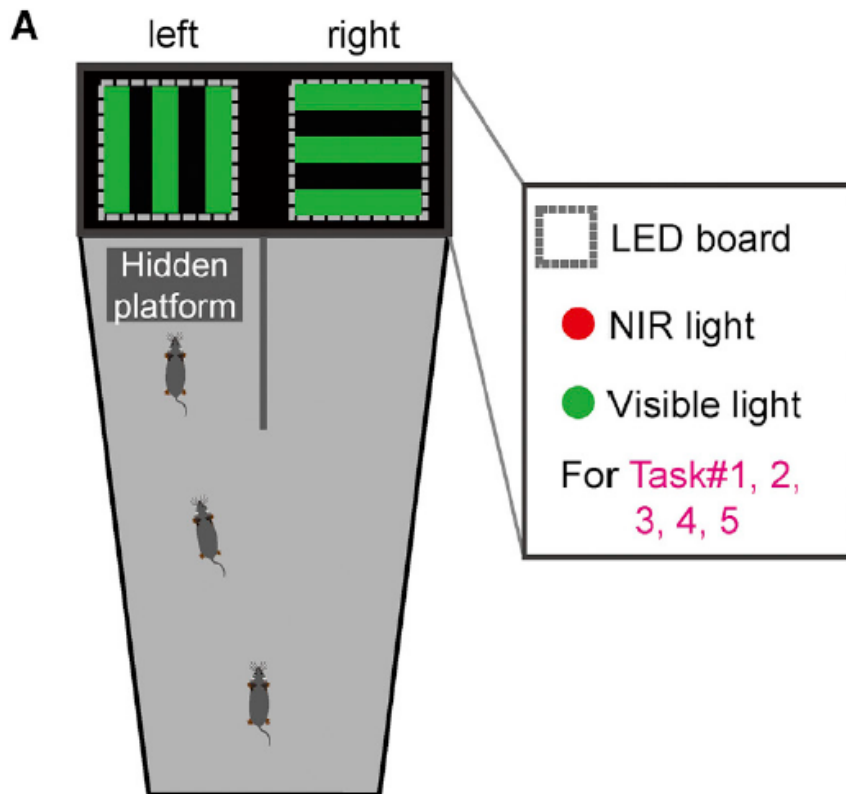


Water maze with platform associated with a light pattern

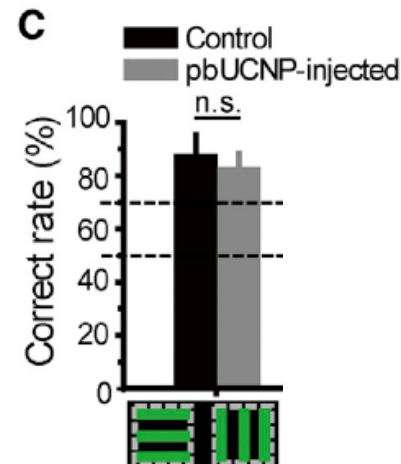
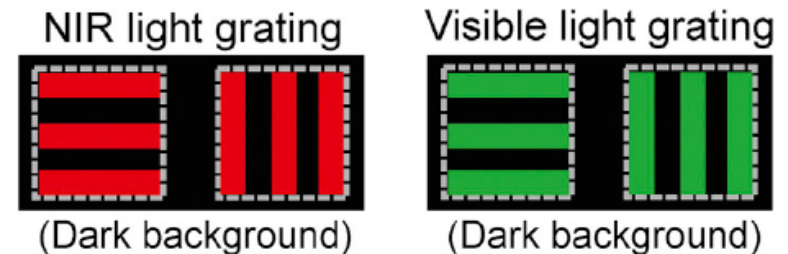
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## **Task#1**



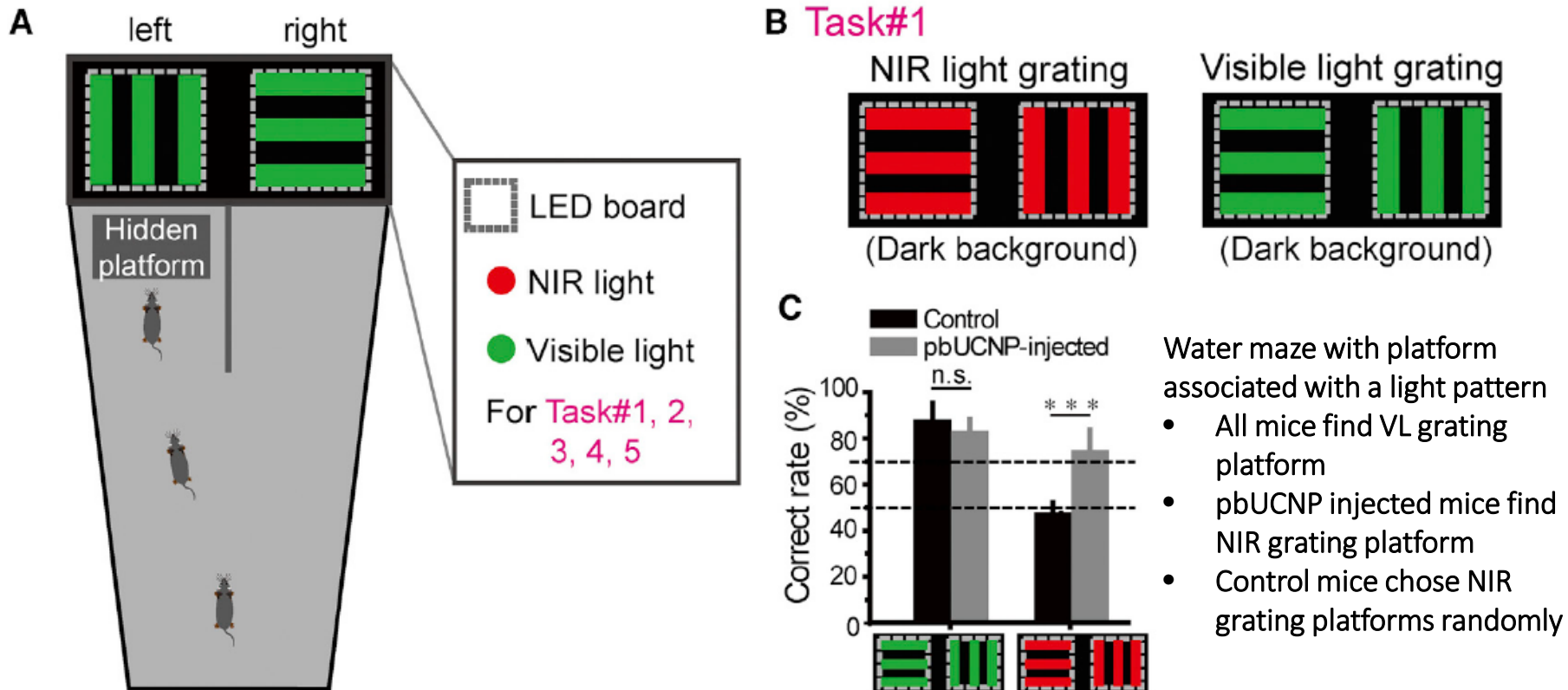
Water maze with platform associated with a light pattern

- All mice find VL grating platform

# photoreceptor-binding upconversion nanoparticles (pbUCNPs)

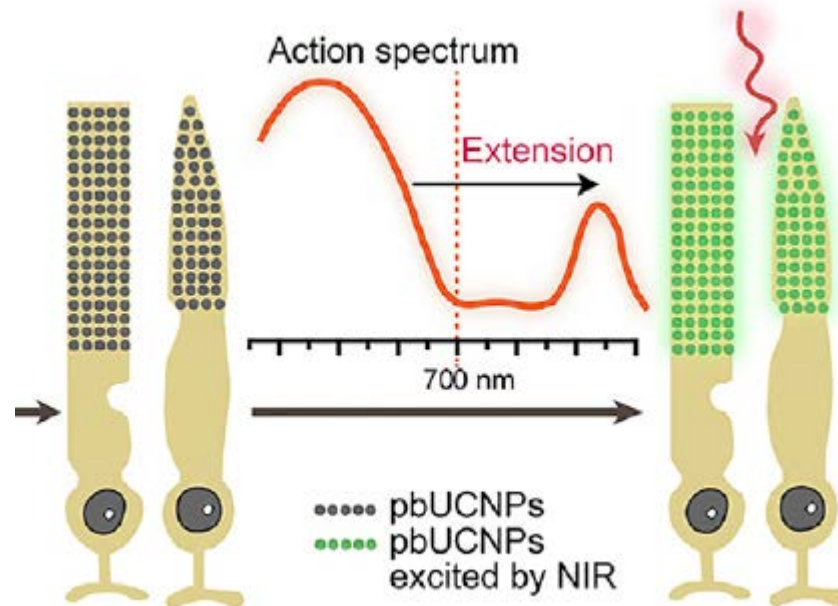
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# photoreceptor-binding upconversion nanoparticles (pbUCNPs)

- Successful extension of the visible light spectrum towards NIR WLs by using nanoantennae added to endogenous visual system
- Both VL and NIR can be seen simultaneously
- Applications in visual repair and enhancement



# Photon upconversion (UC)

CHEMICAL  
REVIEWS

Review

pubs.acs.org/CR

Upconversion Luminescent Materials: Advances and Applications

Jing Zhou,<sup>†</sup> Qian Liu,<sup>†</sup> Wei Feng, Yun Sun, and Fuyou Li\*

## Article

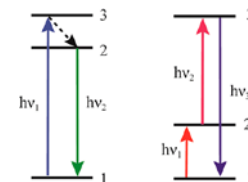
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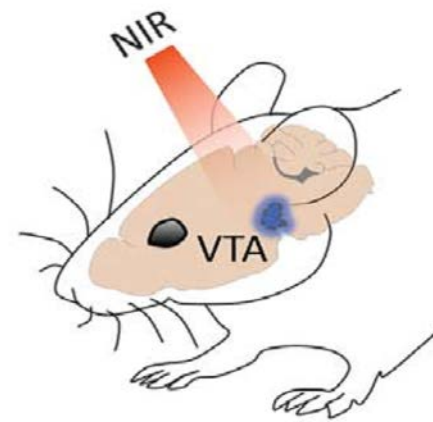
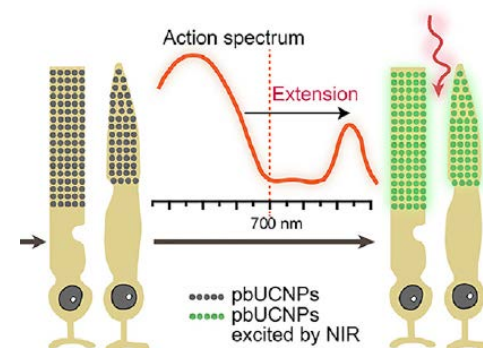
NEUROSCIENCE

### Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics

Shuo Chen,<sup>1\*</sup> Adam Z. Weitemier,<sup>1</sup> Xiao Zeng,<sup>2</sup> Linmeng He,<sup>1</sup> Xiyu Wang,<sup>1</sup> Yanqiu Tao,<sup>1</sup> Arthur J. Y. Huang,<sup>1</sup> Yuki Hashimoto-dani,<sup>3</sup> Masanobu Kano,<sup>3,4</sup> Hirohide Iwasaki,<sup>5</sup> Laxmi Kumar Parajuli,<sup>5</sup> Shigeo Okabe,<sup>5</sup> Daniel B. Loong Teh,<sup>6</sup> Angelo H. All,<sup>7</sup> Iku Tsutsui-Kimura,<sup>8</sup> Kenji F. Tanaka,<sup>8</sup> Xiaogang Liu,<sup>2,9\*</sup> Thomas J. McHugh<sup>1,10\*</sup>



Cell



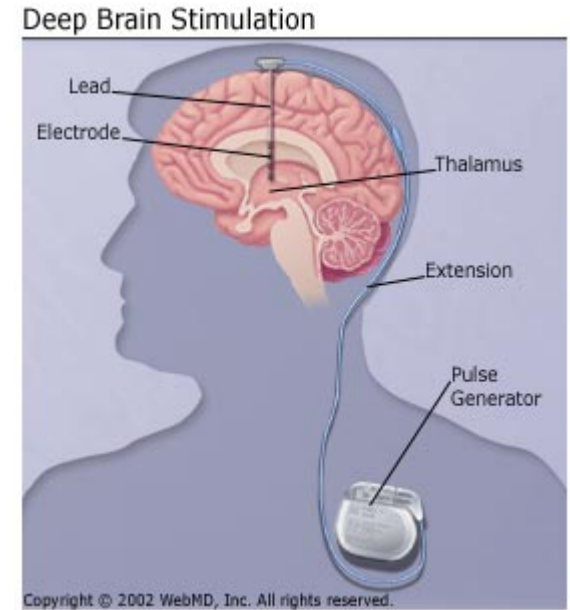


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## Deep brain stimulation

- Promising therapeutic options (e.g. Parkinson's)
- Permanently implanted electrodes
- Non-specific activation of neurons





# Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics

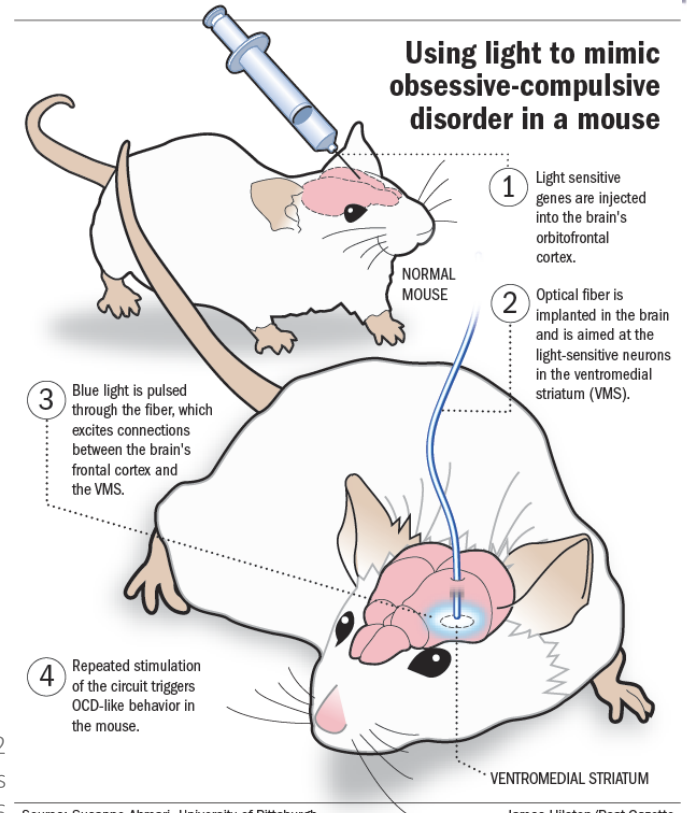
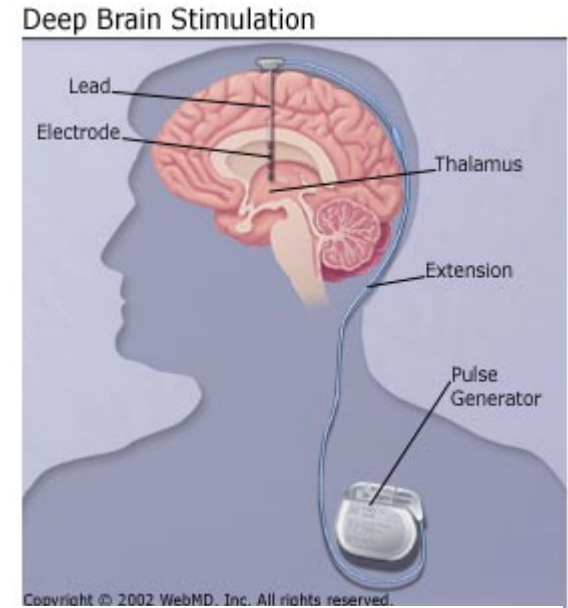
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## Deep brain stimulation

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## Optogenetics

- Cell-specific expression of light activated channels
- Invasive optical fibres (light scattering and absorption)



<https://www.post-gazette.com/news/health/2015/02/01/Pittsburgh-researchers-use-light-on-animal-brains-to-study-mental-disorders/stories/201502010006>

Source: Susanne Ahmari, University of Pittsburgh

James Hilston/Post-Gazette

# Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics

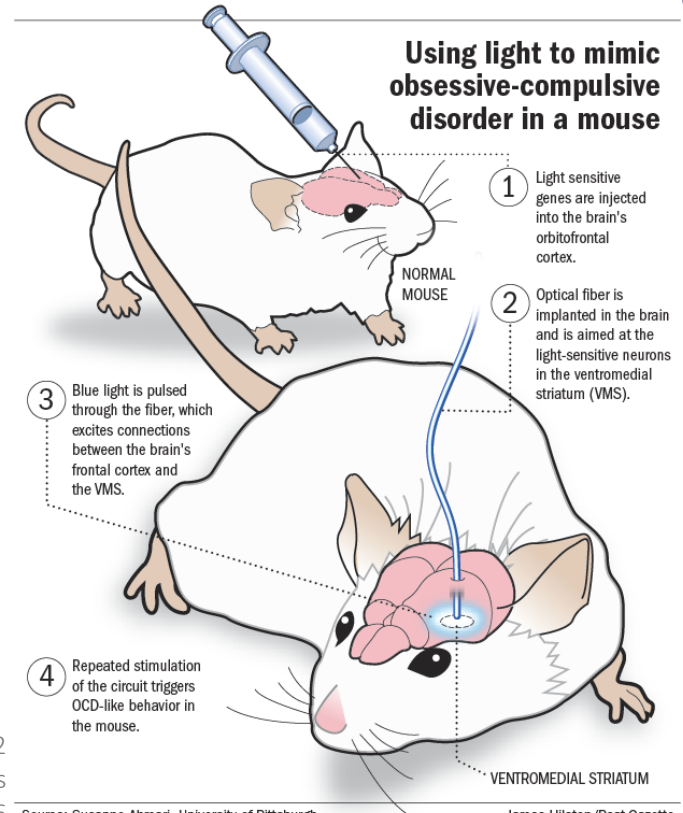
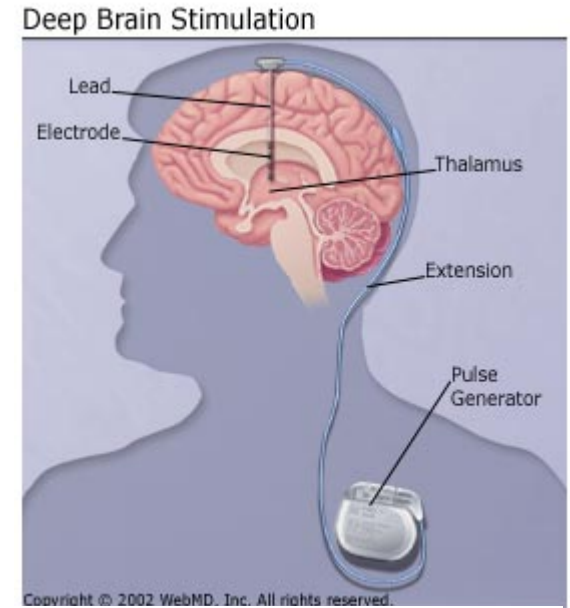
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## Deep brain stimulation

- Promising therapeutic options (e.g. Parkinson's)
- Permanently implanted electrodes
- Non-specific activation of neurons

## Optogenetics

- Cell-specific expression of light activated channels
- Invasive optical fibres (light scattering and absorption)
- Maximum penetration depth is possible with NIR light
- But low energy cannot activate channels
- Two-photon optogenetics only in shallow brain areas (scattering)



<https://www.post-gazette.com/news/health/2015/02/01/Pittsburgh-researchers-use-light-on-animal-brains-to-study-mental-disorders/stories/201502010006>

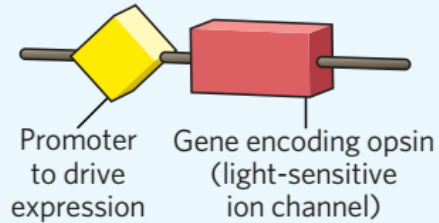
Source: Susanne Ahmari, University of Pittsburgh

James Hilston/Post-Gazette

# “Traditional” optogenetics

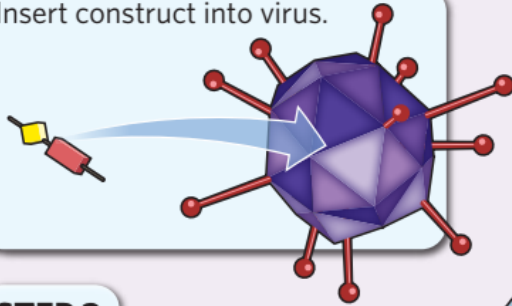
## STEP 1

Piece together genetic construct.



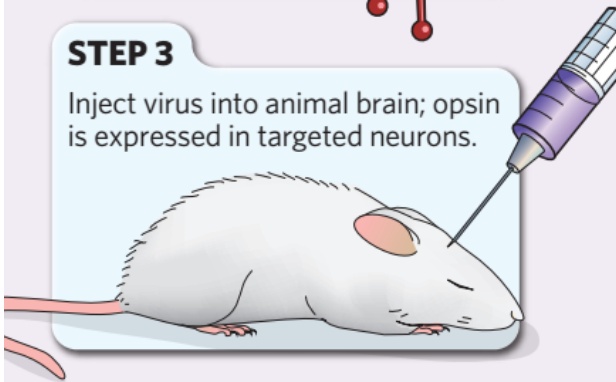
## STEP 2

Insert construct into virus.



## STEP 3

Inject virus into animal brain; opsin is expressed in targeted neurons.



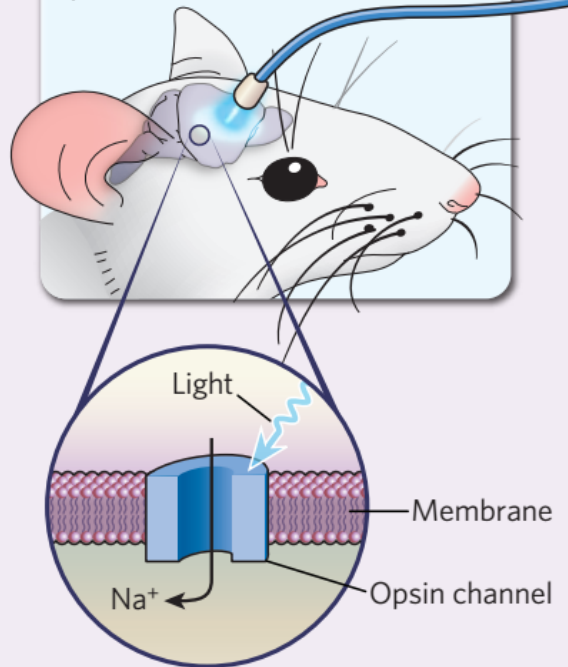
## STEP 4

Insert 'optrode', fibre-optic cable plus electrode.



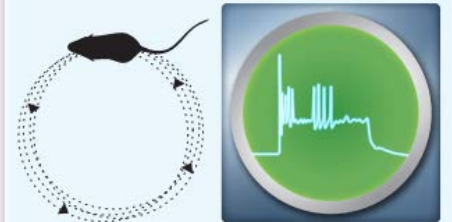
## STEP 5

Laser light of specific wavelength opens ion channel in neurons.



## STEP 6

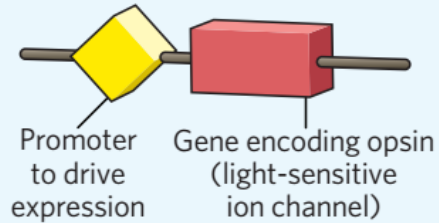
Record electrophysiological and behavioural results.



# UCNP-mediated optogenetics

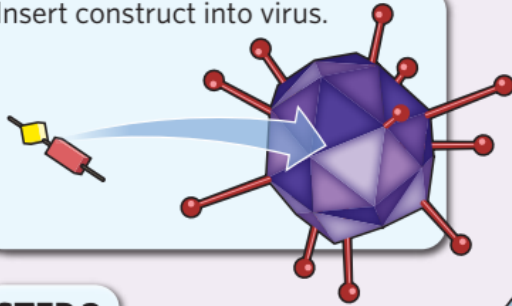
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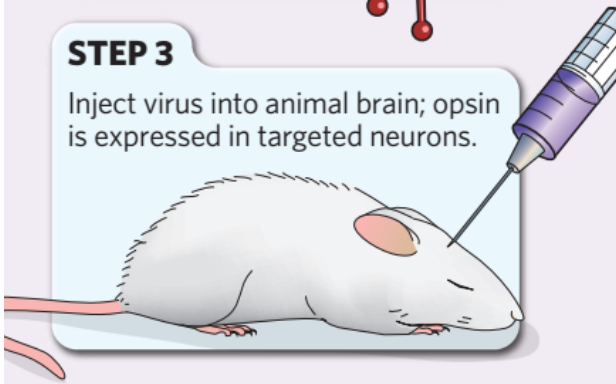
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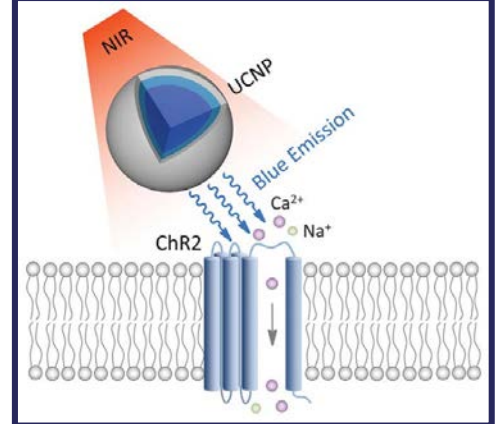
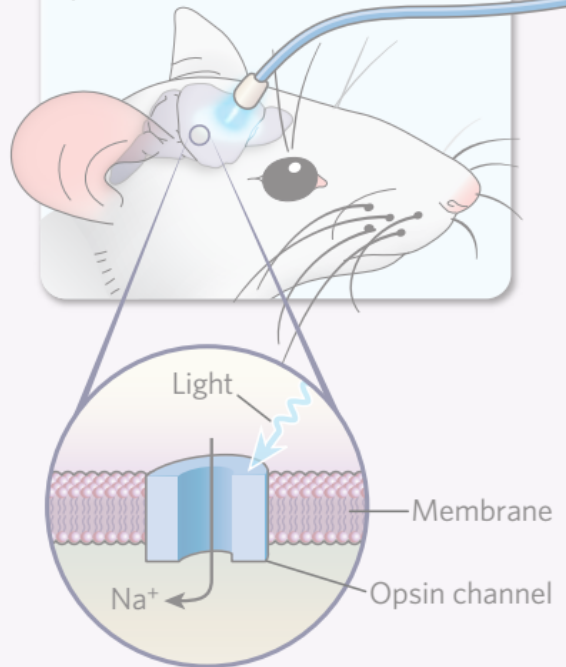
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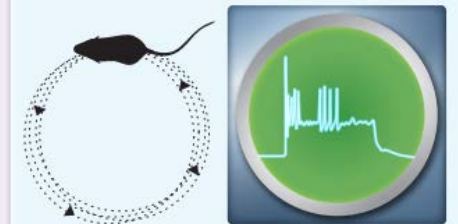
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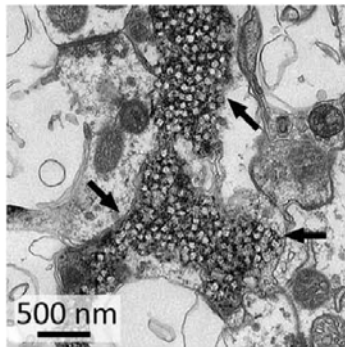
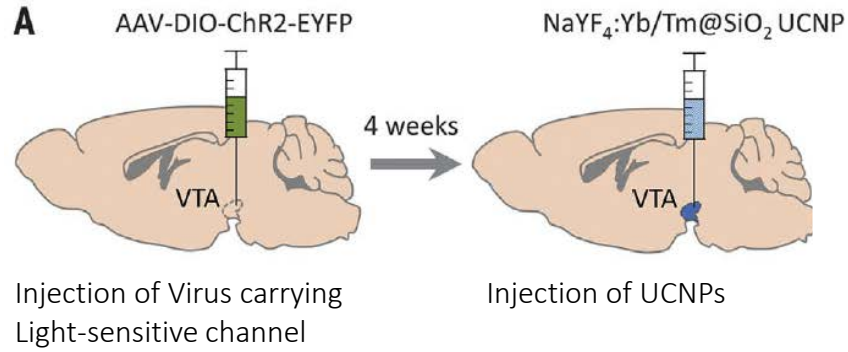
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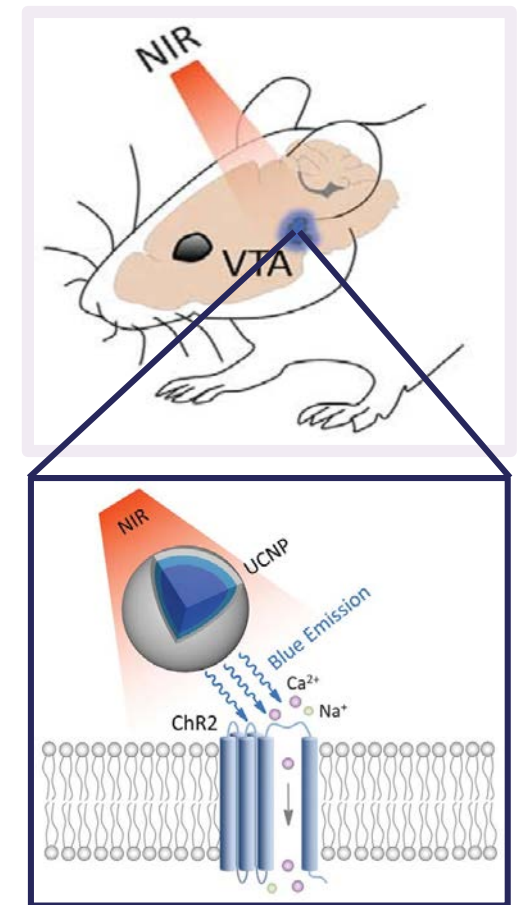




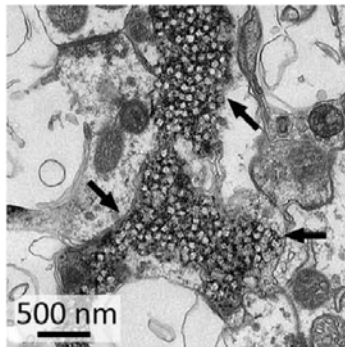
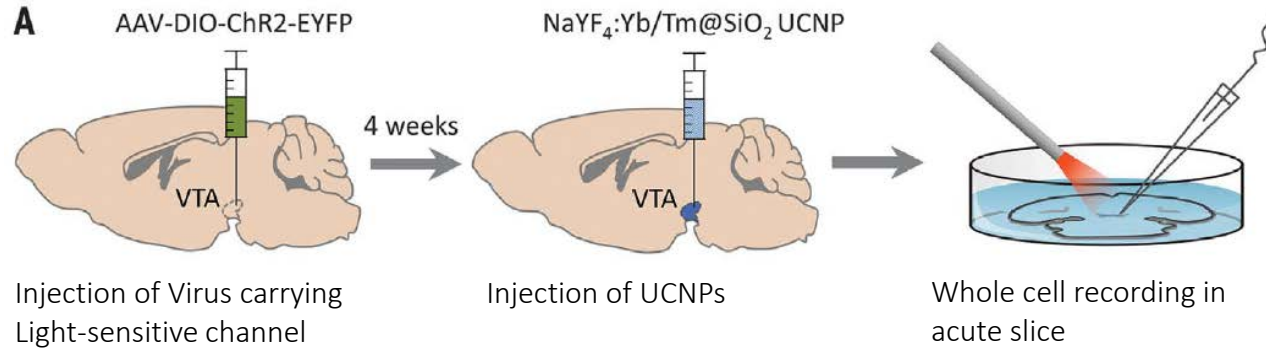
# UCNP-mediated optogenetics



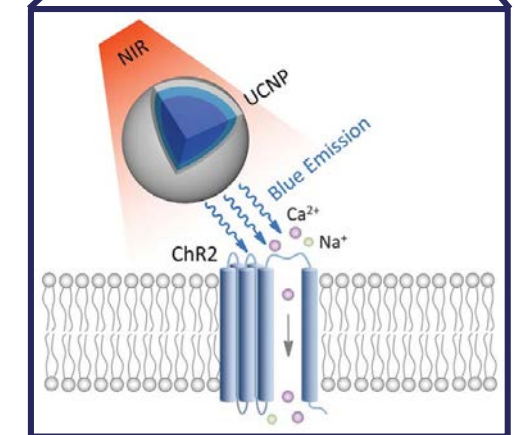
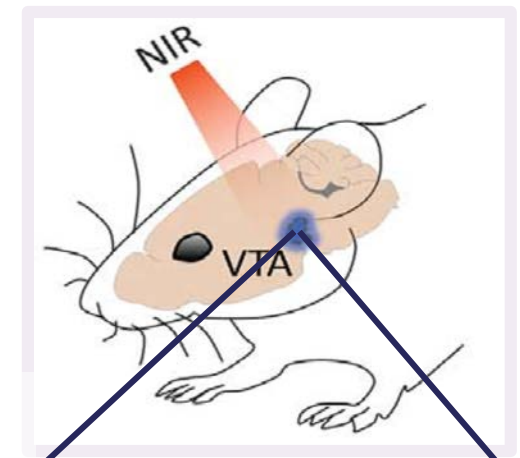
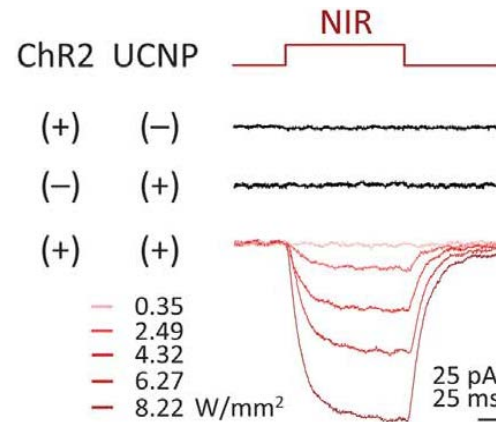
Extracellular localization of injected UCNP



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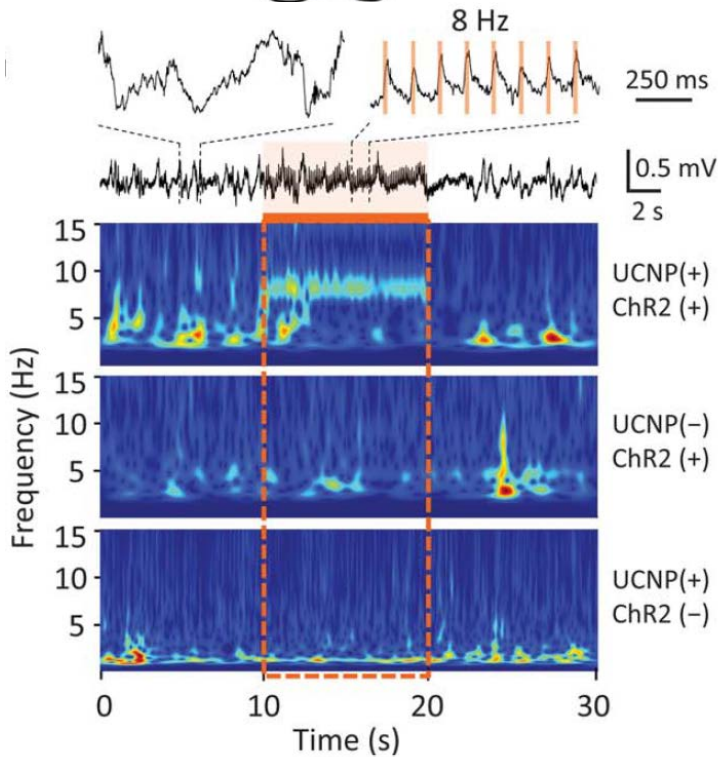
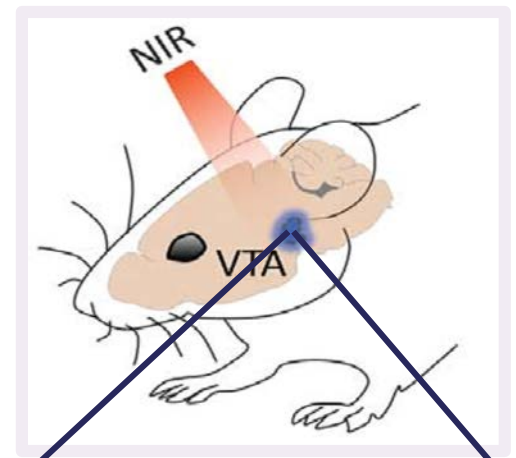
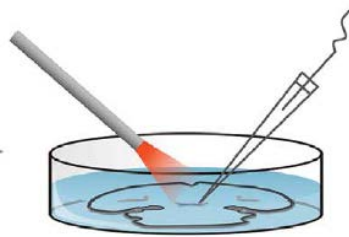
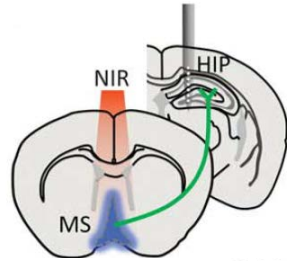


Extracellular localization of injected UCNPs

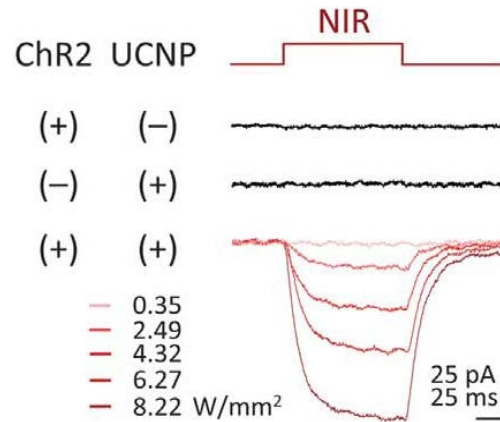


→ NIR evokes current in cells expressing both ChR2 and UCNPs in laser intensity dependent manner

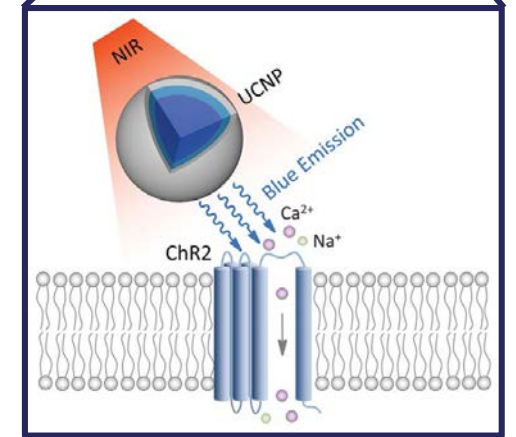
# UCNP-mediated optogenetics



*In vivo* recordings of hippocampal local field potential (LFP)  
 → Pulsed NIR stimulation entrained the hippocampal theta oscillation in a frequency-dependent manner



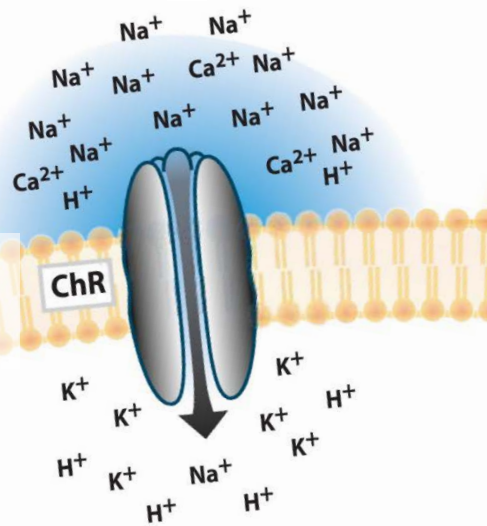
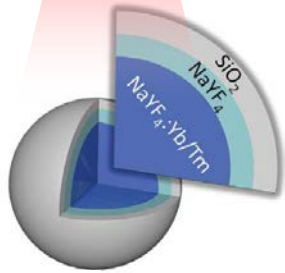
Whole cell recording in acute slice  
 → NIR evokes current in cells expressing both ChR2 and UCNP in laser intensity dependent manner



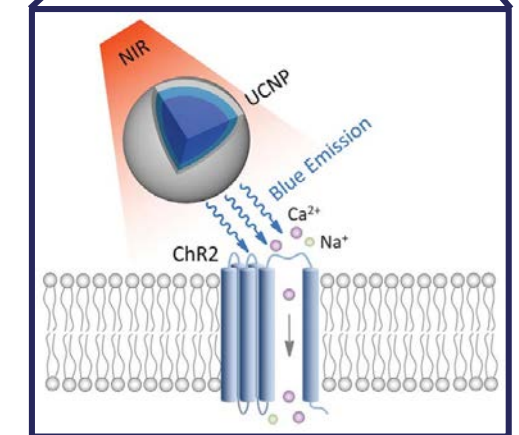
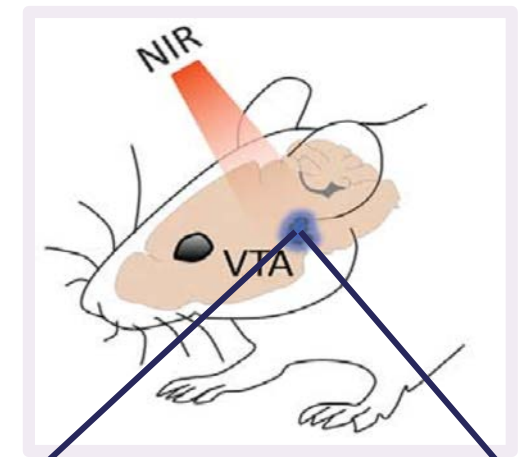
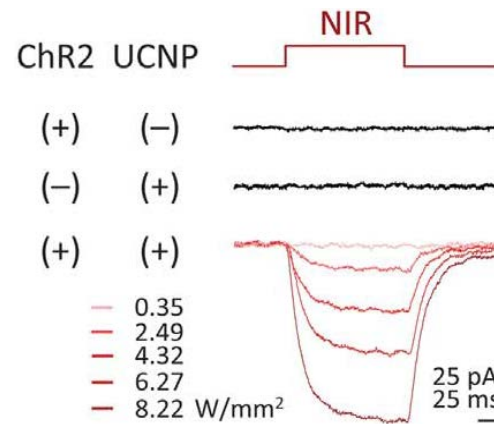


Optic fibre 2 mm above skull

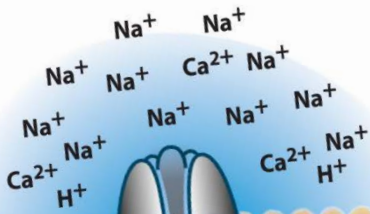
NIR



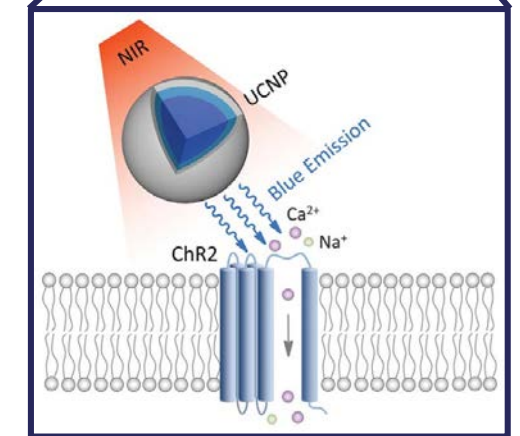
→ Depolarization  
→ More Action Potentials  
= **Excitatory**



**NIR**



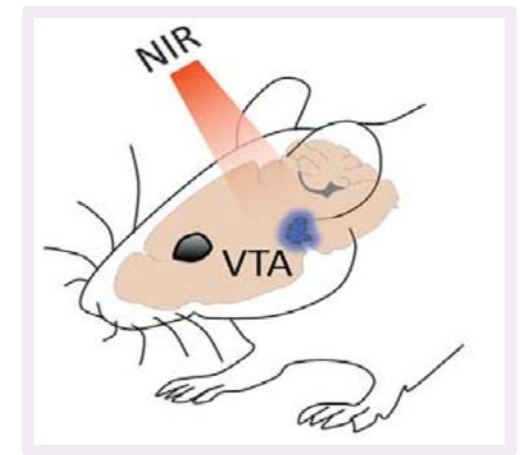
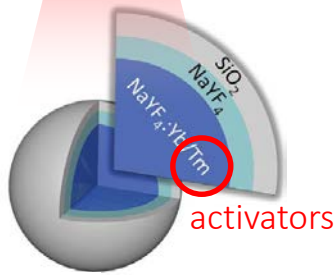
- Hyperpolarization
- Less Action Potentials
- = Inhibition**



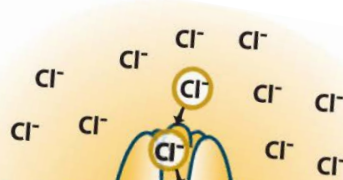
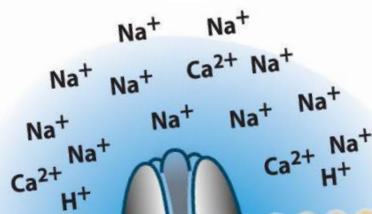
Optic fibre 2 mm above skull

NIR

NIR



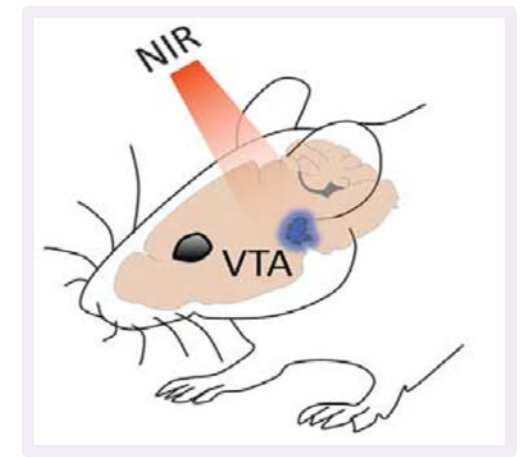
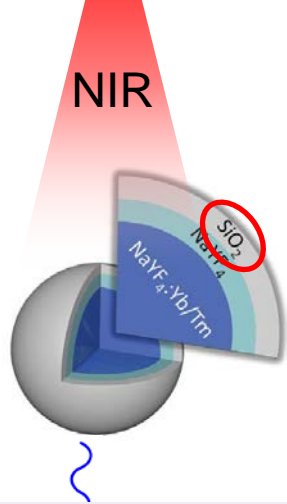
Incorporation of another element into the UCNP **shifts emission WL**  
→ Specific activation of one type of channel  
→ Specific **activation or inhibition** of specific neuron



Halorhodopsin (NpHR)  
Archaerhodopsin (Arch)

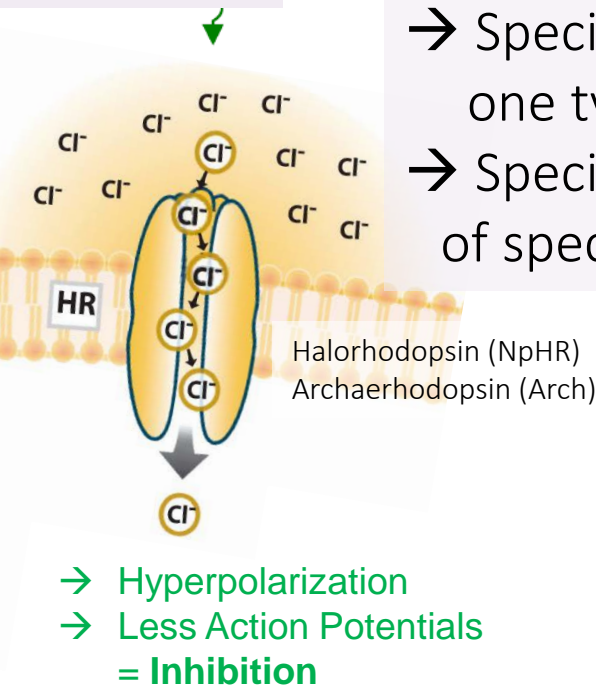
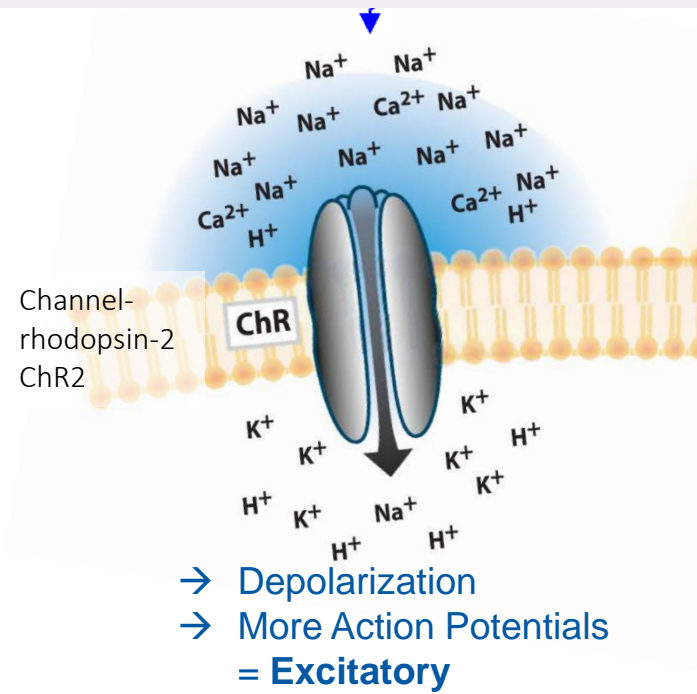
→ Depolarization  
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= **Excitatory**

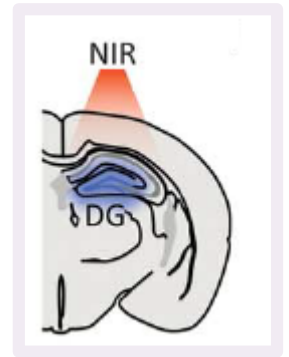
→ Hyperpolarization  
→ Less Action Potentials  
= **Inhibition**



**Biocompatibility** further optimized by Silica Coating (NaYF<sub>4</sub>:Yb/Tm@SiO<sub>2</sub>)

Incorporation of another element into the UCNP **shifts emission WL**  
 → Specific activation of one type of channel  
 → Specific **activation or inhibition** of specific neuron





## LETTER

doi:10.1038/nature11028

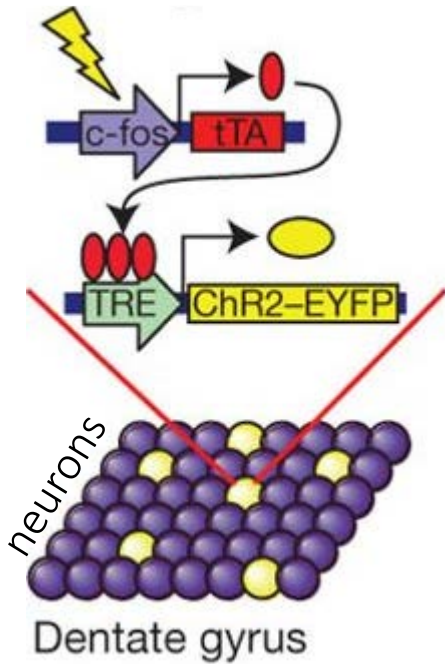
### Optogenetic stimulation of a hippocampal engram activates fear memory recall

Xu Liu<sup>1\*</sup>, Steve Ramirez<sup>1\*</sup>, Petti T. Pang<sup>1</sup>, Corey B. Puryear<sup>1</sup>, Arvind Govindarajan<sup>1</sup>, Karl Deisseroth<sup>2</sup> & Susumu Tonegawa<sup>1</sup>

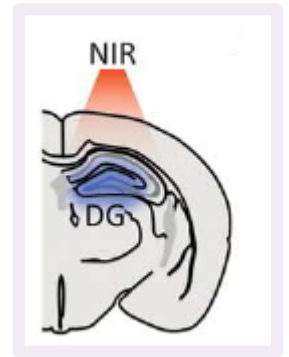
- Memory (engram) = encoded by a sparse population of neurons
- Neurons can be tagged during learning
- Activation of those neurons → respective behavioural output  
E.g. freezing in fear conditioning
- Here: optogenetic reactivation of hippocampal neurons activated during fear conditioning induces freezing behaviour



# *In vivo* alteration of behaviour using UCNP-mediated optogenetics

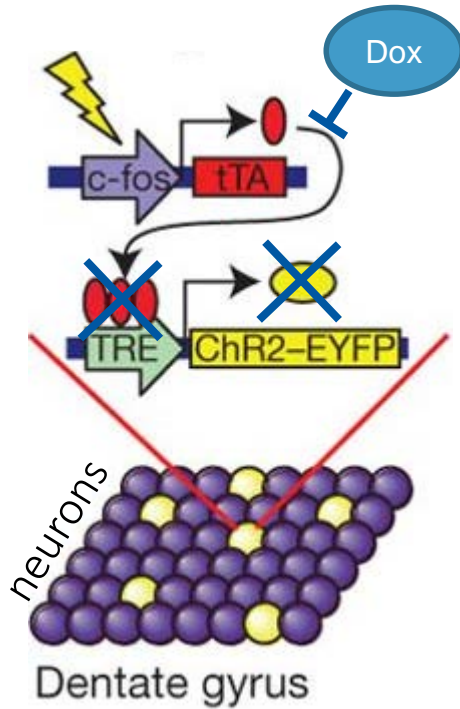


- C-fos is expressed upon neuronal activity ⚡
- Mice carry tetracycline transcriptional activator (**tTA**) under **c-fos** promoter
- tTA binds tetracycline-responsive element (**TRE**) site, triggering expression of Channelrhodopsin (**ChR2**, tagged with **EYFP**)

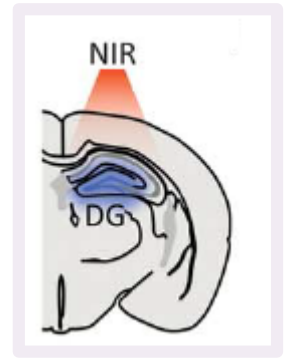




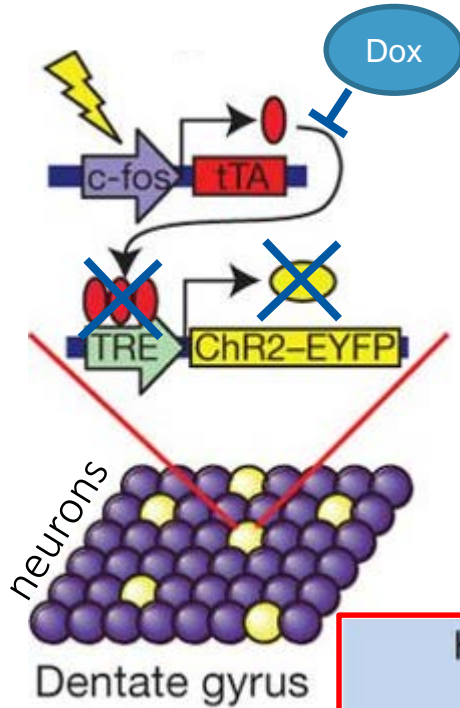
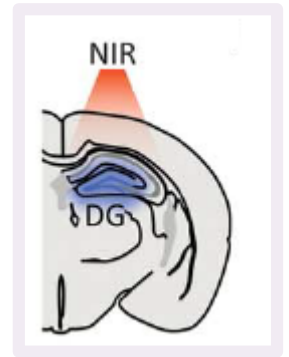
# *In vivo* alteration of behaviour using UCNP-mediated optogenetics



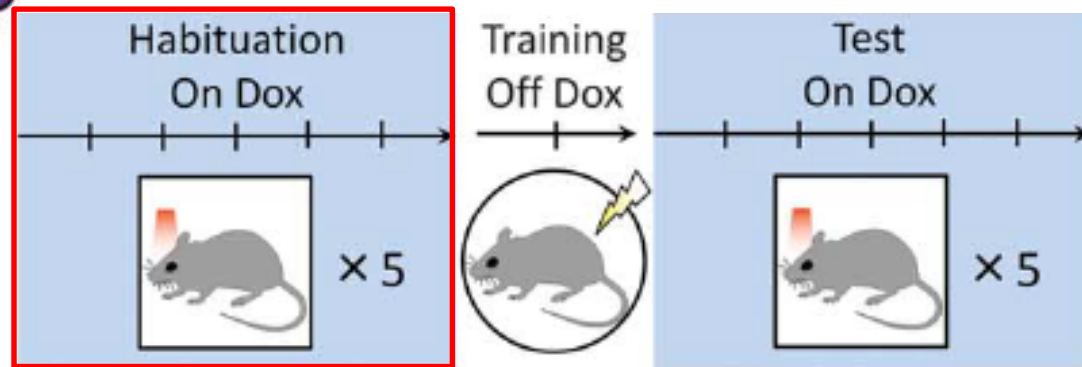
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- **Tetracycline Off System:** +Doxycycline = no ChR expression



# *In vivo* alteration of behaviour using UCNP-mediated optogenetics

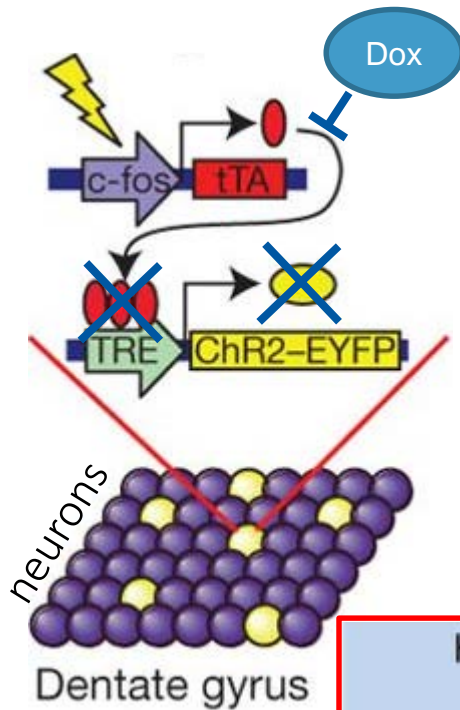
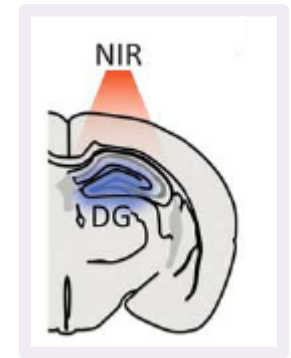


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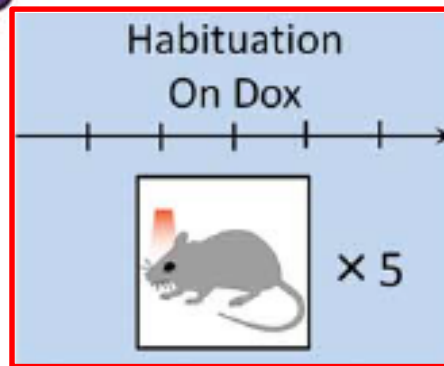


- No ChR-expression (+Dox)
- UCNPs have been injected (but no effect, as no channel)
- **Environment A**: freezing reaction upon NIR illumination is tested

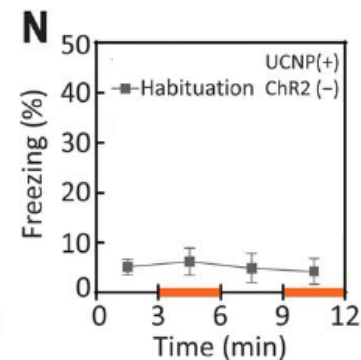
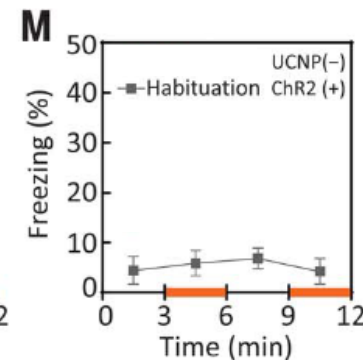
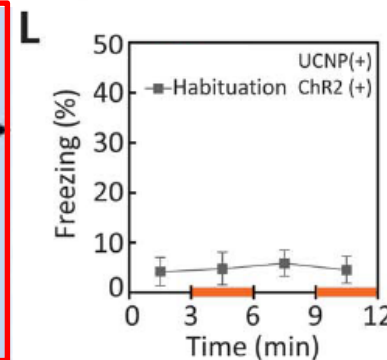
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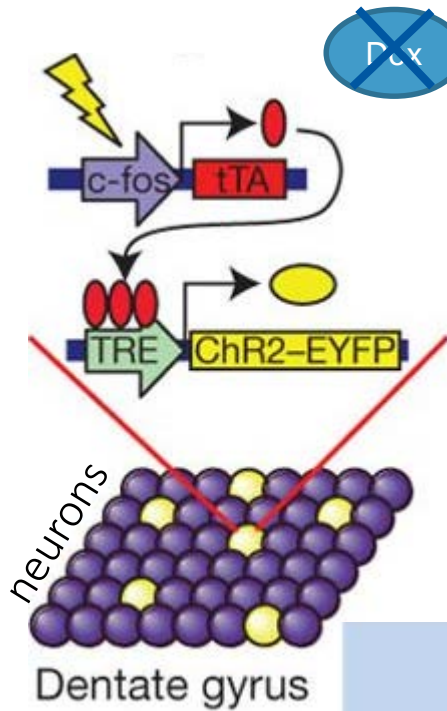
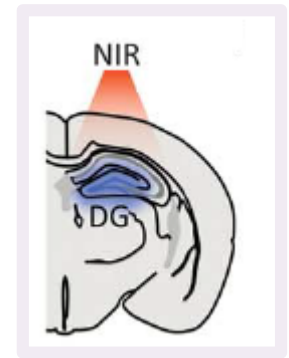
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- **Tetracycline Off System:** +Doxycycline = no ChR expression



- No ChR-expression (+Dox)
- UCNP have been injected (but no effect, as no channel)
- **Environment A:** freezing reaction upon NIR illumination is tested



# *In vivo* alteration of behaviour using UCNP-mediated optogenetics

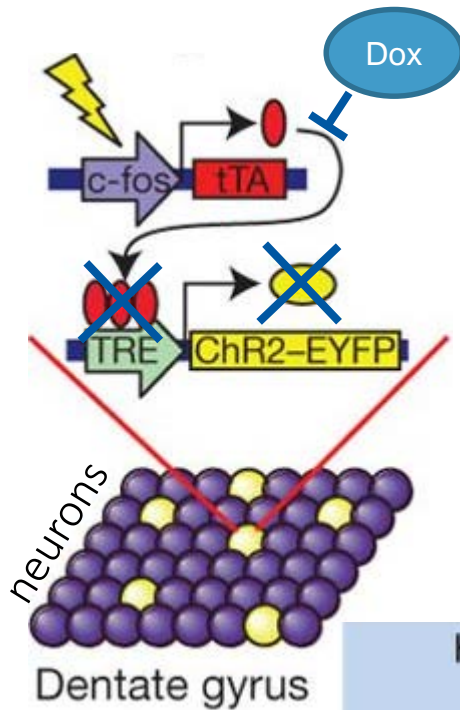
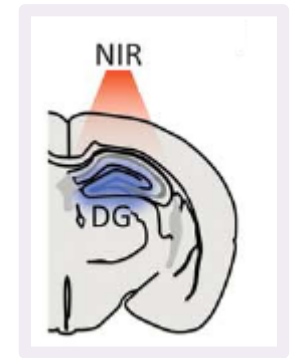


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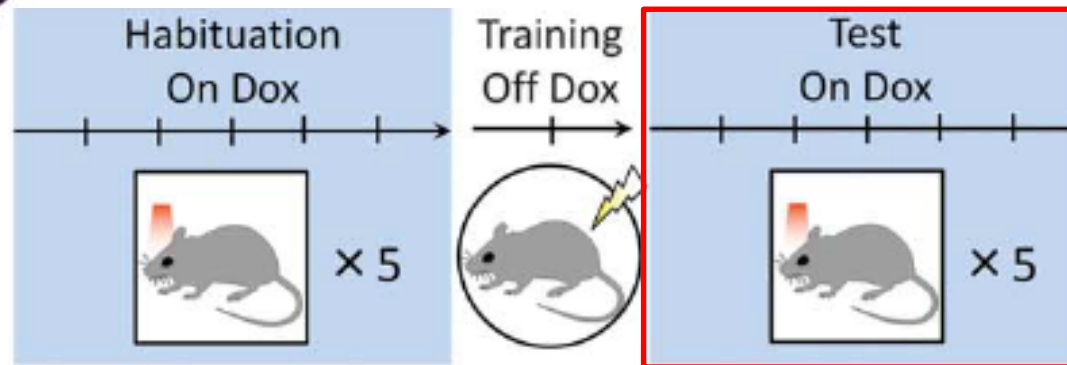


- Training in environment B: fear conditioning using electric shocks
- **ChR-expression** in the active neurons ⚡ (-Dox)
- UCNPs have been injected before (but no effect, as no NIR illumination)

# *In vivo* alteration of behaviour using UCNP-mediated optogenetics



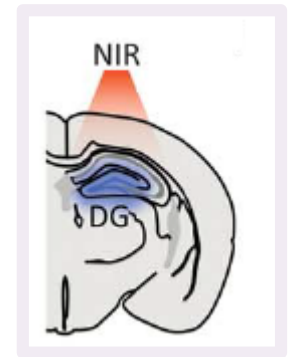
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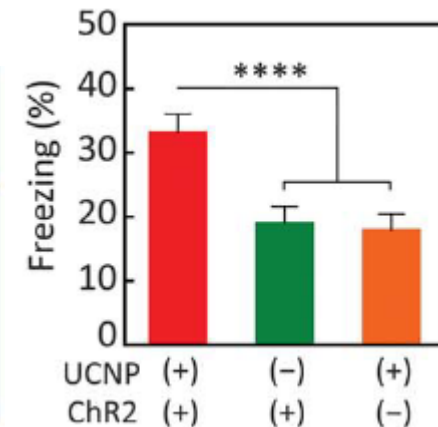
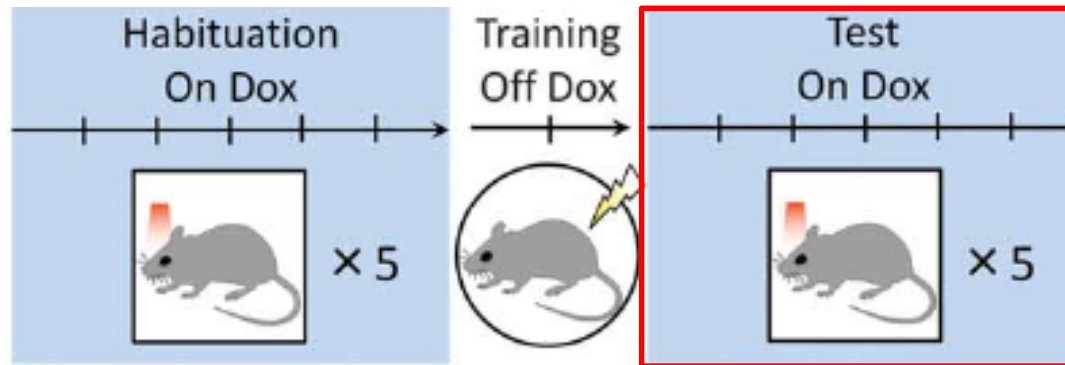
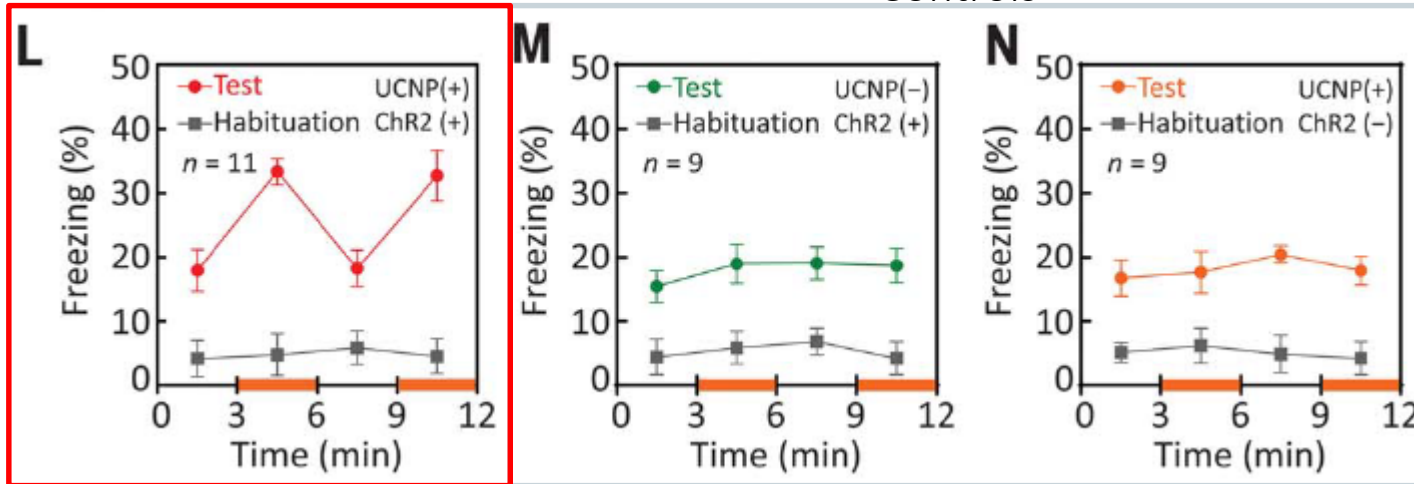
- No new ChR-expression (+Dox) → only the cells that have been active during fear conditioning, are equipped with channels
- UCNPs have been injected before → freezing reaction upon **NIR illumination** is tested
- **Environment A**: is not associated with fear



# *In vivo* alteration of behaviour using UCNP-mediated optogenetics



Controls

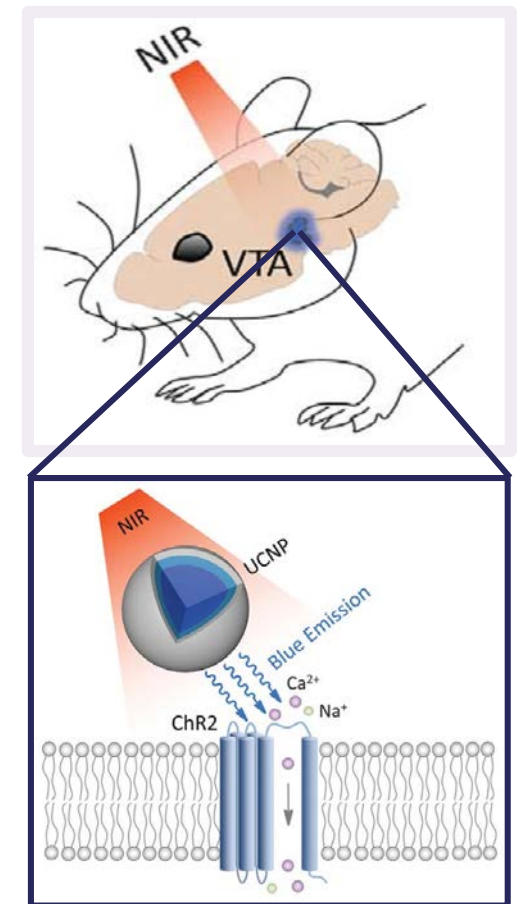


- No new ChR-expression (+Dox) → only the cells that have been active during fear conditioning, are equipped with channels
- UCNP have been injected before → freezing reaction upon NIR illumination is elevated
- Environment A: is not associated with fear



# UCNP-mediated optogenetics

- Successful activation or inhibition of specific neuronal populations (spectral tuning of UCNP)
- Successful implementation *in vivo* (biocompatible and long-term stability)
- Minimally invasive technique to change behaviour
- Potential in «remote» therapies for neurological disorders



# Photon upconversion (UC)

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## Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae

Yuqian Ma,<sup>1,5</sup> Jin Bao,<sup>1,2,5,\*</sup> Yuanwei Zhang,<sup>3,5</sup> Zhanjun Li,<sup>3</sup> Xiangyu Zhou,<sup>1</sup> Changlin Wan,<sup>1</sup> Ling Huang,<sup>3</sup> Yang Zhao,<sup>3</sup> Gang Han,<sup>3,\*</sup> and Tian Xue<sup>1,2,4,5,\*</sup>

## Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics

Shuo Chen,<sup>1\*</sup> Adam Z. Weitemier,<sup>1</sup> Xiao Zeng,<sup>2</sup> Linmeng He,<sup>1</sup> Xiyu Wang,<sup>1</sup> Yanqiu Tao,<sup>1</sup> Arthur J. Y. Huang,<sup>1</sup> Yuki Hashimoto<sup>2,3</sup>, Masanobu Kano,<sup>3,4</sup> Hirohide Iwasaki,<sup>5</sup> Laxmi Kumar Parajuli,<sup>5</sup> Shigeo Okabe,<sup>5</sup> Daniel B. Loong Teh,<sup>6</sup> Angelo H. All,<sup>7</sup> Iku Tsutsui-Kimura,<sup>8</sup> Kenji F. Tanaka,<sup>8</sup> Xiaogang Liu,<sup>2,9\*</sup> Thomas J. McHugh<sup>1,10\*</sup>

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## Near-infrared light induced *in vivo* photodynamic therapy of cancer based on upconversion nanoparticles

Chao Wang, Huiquan Tao, Liang Cheng, Zhuang Liu\*

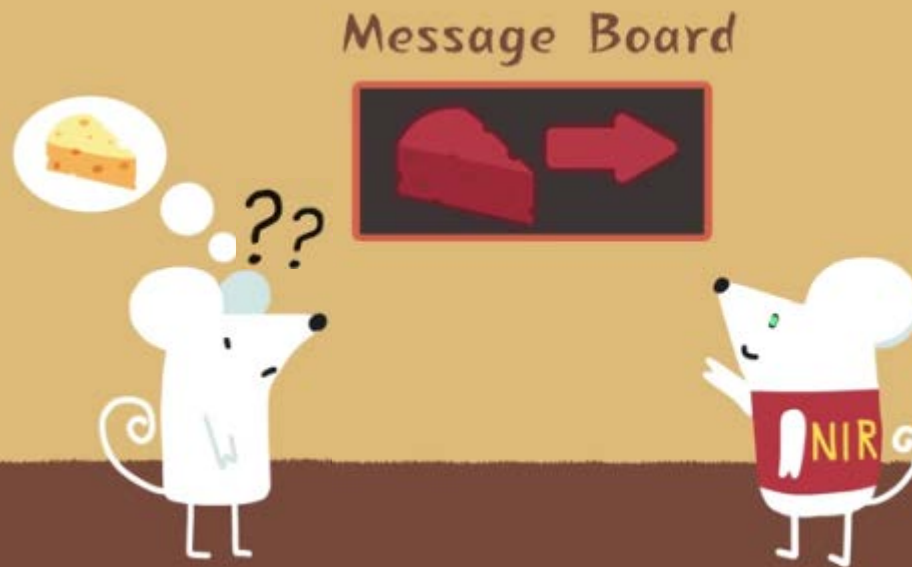
## Dual-modality *in vivo* imaging using rare-earth nanocrystals with near-infrared to near-infrared (NIR-to-NIR) upconversion luminescence and magnetic resonance properties

Jing Zhou<sup>a</sup>, Yun Sun<sup>a</sup>, Xiaoxia Du<sup>b</sup>, Liqin Xiong<sup>a</sup>, He Hu<sup>a</sup>, Fuyou Li<sup>a,\*</sup>

## Photon upconversion facilitated molecular solar energy storage†

Karl Börjesson,<sup>a</sup> Damir Dzebo,<sup>b</sup> Bo Albinsson<sup>b</sup> and Kasper Moth-Poulsen<sup>\*a</sup>

# Upconversion Nanoparticles (UCNPs) in Neuroscience



Journal Club, 16th April 2019

Alexandra Bentrup