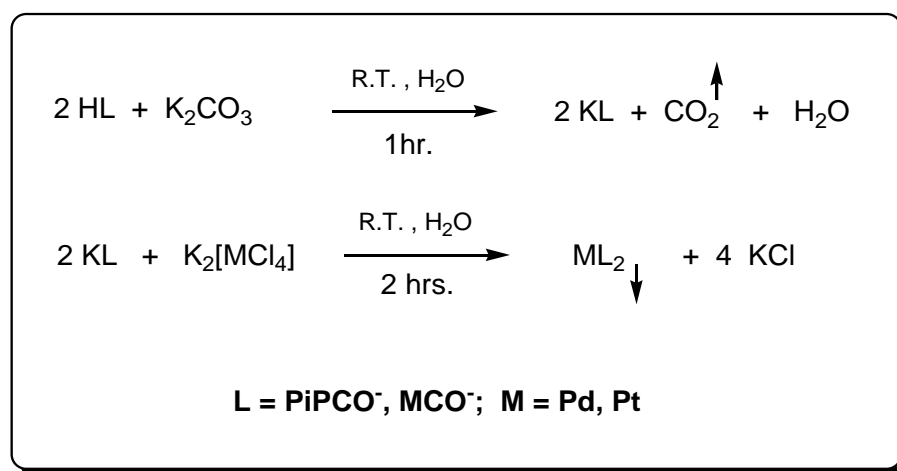
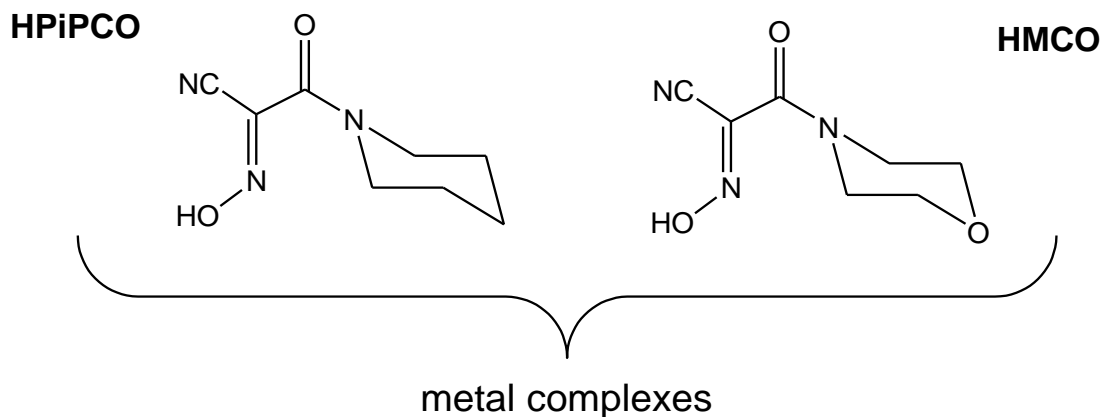




## **Jessica Ratcliff: MS 2007**

**Thesis**      "Further Investigations of Cytotoxic Metallocyanoximates"

Jessica's research project was dedicated to continuation of studies of *in vitro* cytotoxicity of two earlier reported by Daniel Eddings Pd(II) and Pt(II) complexes with N-substituted acetamide-cyanoximes HPiCO and HMCO (see Daniel Eddings section of this web page) as shown in Figure 1. Actual photographs of fine powders of PtL<sub>2</sub>, that have highly unusual for Pt(II) dark green color, are displayed in Figure 2. These stoichiometric ML<sub>2</sub> composition (L = deprotonated PiPCO<sup>-</sup> and MCO<sup>-</sup> anions) were tested *in vitro* against HeLa (cervical) and colon (WiDR) human cancer cell lines using cisplatin as positive control. Studied complexes are comparable in cytotoxicity to that of cisplatin. DNA binding properties of these compounds has been investigated.



**Figure 1.** Eddings' cyanoximes and preparation of their metal complexes.

The justification for conducted investigation follows. It has been found that several compounds of platinum (II, IV) as well as palladium(II) are well-established as inorganic anticancer pharmaceuticals (see description below). At the same time substantial biological activity (growth regulating, antimicrobial, anticancer, pesticide detoxifying) has also been demonstrated during the last two decades for the cyanoximes - compounds having general formula NC-C(R)=NOH, where R is an electron withdrawing group. Therefore, studies are underway that are directed towards combining the useful properties of both classes of compounds in order to create a new group of antitumor agents that may have lesser side effects and general toxicity and better solubility than cisplatin family of metal-based anticancer drugs.

At the same time obtained Pt(II) acetamide-cyanoximates demonstrated highly unusual physico-chemical properties which inspired us on their detailed studies briefly described below.

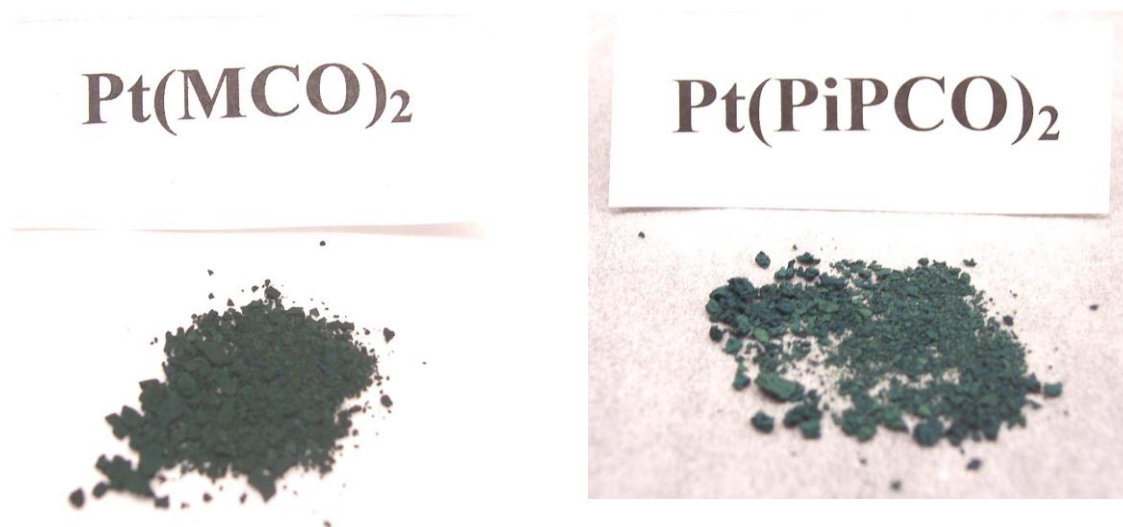
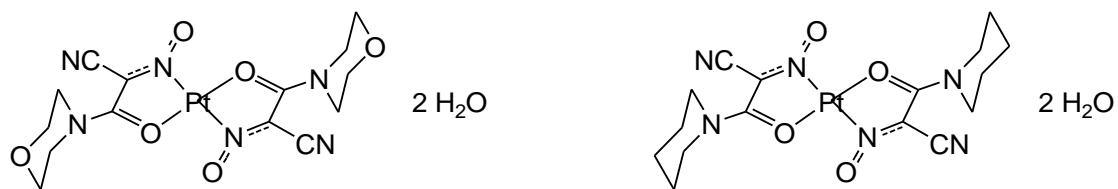


Figure 2. Actual photographs of cytotoxic bivalent platinum acetamide-cyanoximates.

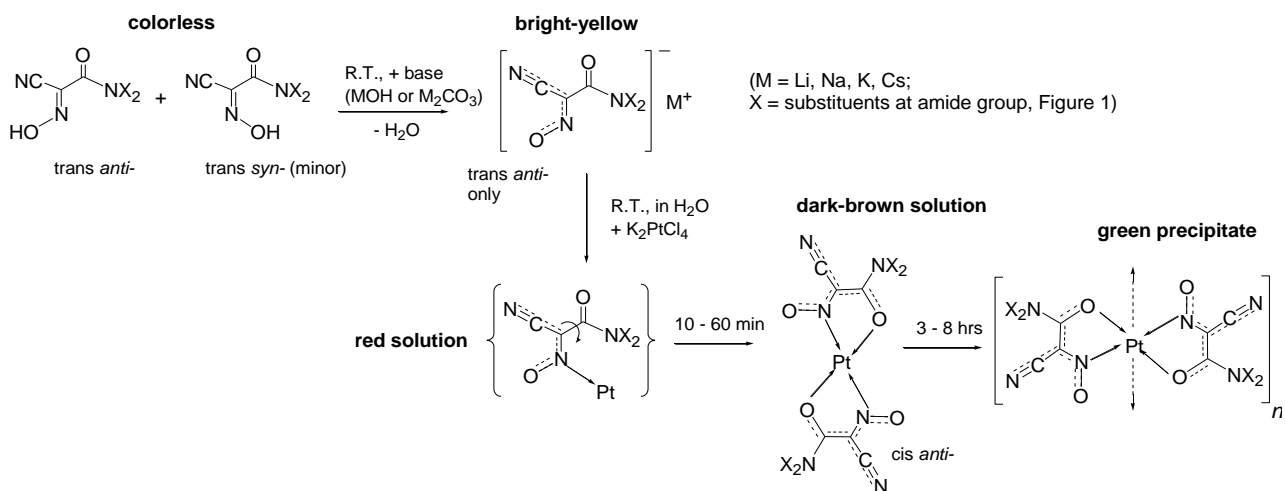


Figure 3. Developed route to green  $\pi$ -stacked Pt(II)-acetamidecyanoximates.

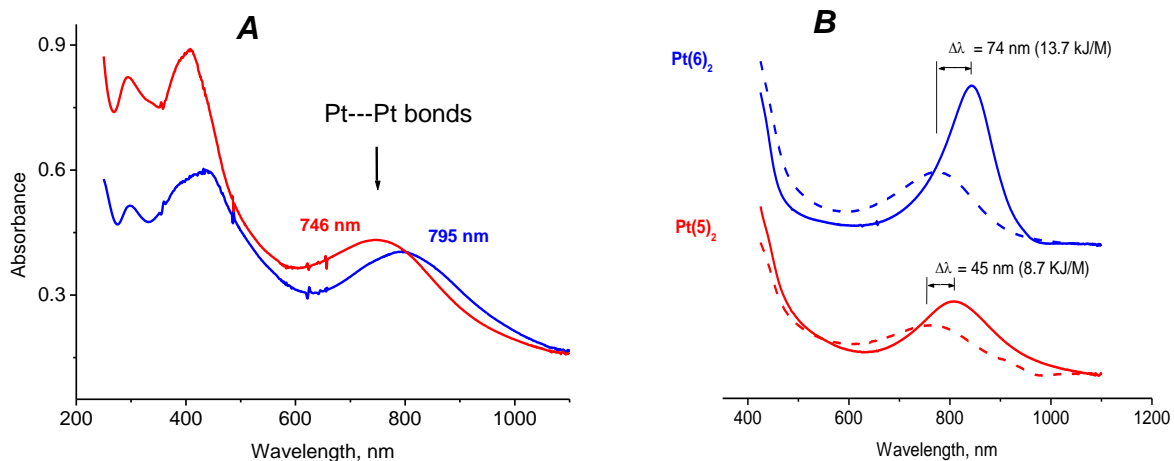


Figure 4. (A) - Solid-state UV-visible spectra of  $\text{Pt}(\text{PiPCO})_2$  (blue) and  $\text{Pt}(\text{MCO})_2$  (red) recorded as fine suspensions in silicon oil, and (B) - overlaid UV-visible spectra of green saturated solutions of nanometer-size one dimensional Pt---Pt stacks showing their pronounced solvatochromism. Blue: solid line – EtOAc, dashed – formamide solutions. Red: solid line – diethylacetamide, dashed – EtOH.

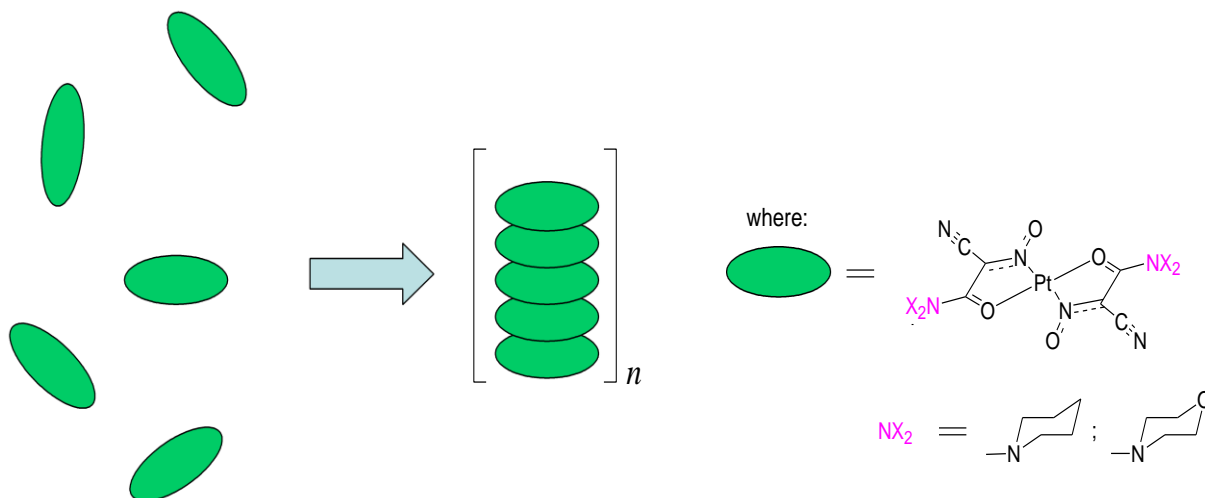
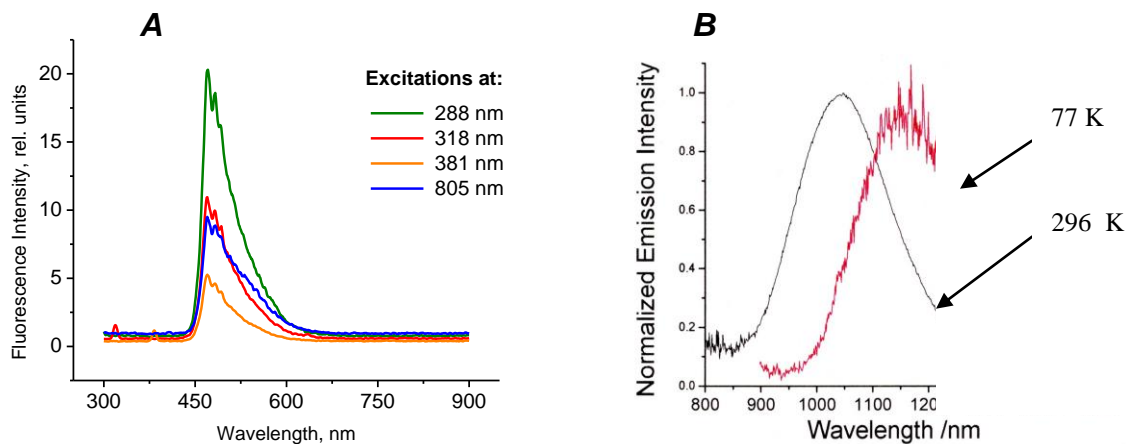
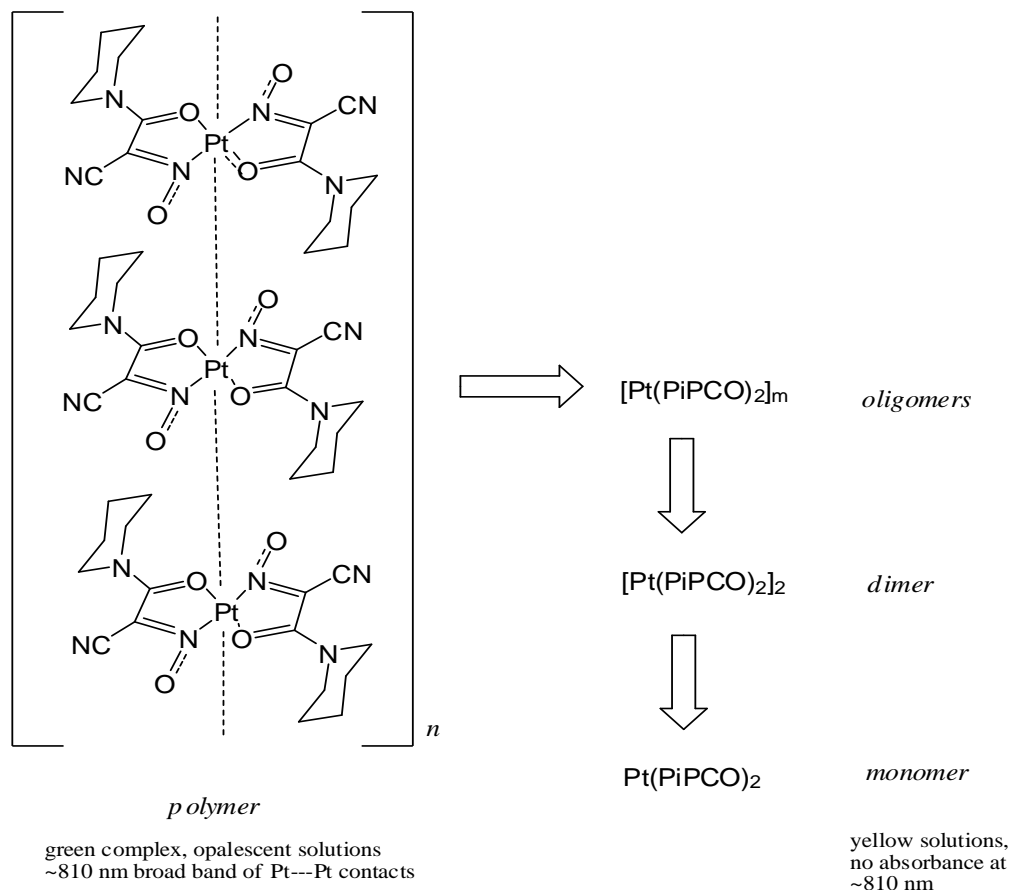


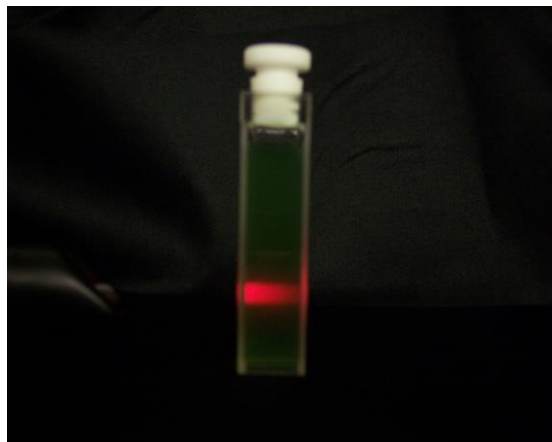
Figure 5. Aggregation of complexes in solutions and suggested one dimensional "poker-chips" type Pt---Pt stacks based on the acetamidedecyanoximes MCO<sup>-</sup> and PiPCO<sup>-</sup>.



**Figure 6.** Ligand-based fluorescence spectra of emerald-green polymeric Pt(PiPCO)<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> solution (A) recorded at different excitation wavelengths, and metal-based fluorescence of solid sample (B).



**Figure 7.** Disaggregation of multi-nanometer size Pt---Pt stacks in solutions by coordinating donor solvents such as DMSO, pyridine, 2-picoline.



**A**

1 drop of quenching DMSO solvent is added into the cuvette:



**B**

**Figure 8:** Actual photographs of  $\text{Pt}(\text{MCO})_2$  in solutions. (A): the Tyndall effect in aggregated opalescent green solutions of  $\text{Pt}(\text{MCO})_2$  in DMF showing significant light scattering; B – the monomeric species of  $\text{Pt}(\text{MCO})_2$  in the same solution after addition of DMSO.

## Results of *in vitro* investigations of the biological activity of Pd/Pt complexes

**Antiproliferative Activity Studies.** The cytotoxicity study of  $\text{Pt}(\text{MCO})_2 \cdot 2\text{H}_2\text{O}$  and  $\text{Pd}(\text{MCO})_2$  revealed that these two compounds are comparable in cytotoxicity to cisplatin.  $\text{Pd}(\text{MCO})_2$  and  $\text{Pt}(\text{MCO})_2 \cdot 2\text{H}_2\text{O}$  were tested at 1.0 mM, 0.1 mM, 0.01 mM, and 0.001 mM concentrations in both HeLa (cervical cancer) and WiDr (colon cancer) cell lines.  $\text{Pd}(\text{MCO})_2$  has repeatedly shown a higher activity against HeLa and WiDr cells than that of  $\text{Pt}(\text{MCO})_2 \cdot 2\text{H}_2\text{O}$ .

The cytotoxicity study found that  $\text{Pt}(\text{MCO})_2 \cdot 2\text{H}_2\text{O}$  and  $\text{Pd}(\text{MCO})_2$  affected HeLa cells greatly at 1.0 mM concentrations showing  $42\% \pm 3\%$  and  $45\% \pm 3\%$  cell death respectively. These results were comparable to values obtained with cisplatin, at 1 mM, which was used as a positive control, showing a  $56\% \pm 5\%$  cell death against HeLa cells. Results are statistically averaged after three independent trials.

Both  $\text{Pt}(\text{MCO})_2 \cdot 2\text{H}_2\text{O}$  and  $\text{Pd}(\text{MCO})_2$  affected WiDr cells causing  $73\% \pm 9\%$  and  $81\% \pm 11\%$  cell death respectively at 1.0 mM. At the same concentration, cisplatin caused  $64\% \pm 1\%$  of cell death under the same conditions. This finding is a bit surprising since colon cancer cells are reportedly more resistant towards chemical agents than HeLa cells. Metallo cyanoximates were also found to be cytotoxic at 0.1 mM concentration. At 0.1 mM,  $\text{Pt}(\text{MCO})_2 \cdot 2\text{H}_2\text{O}$  caused 20% cell death, while the palladium analogue,  $\text{Pd}(\text{MCO})_2$ , caused 16% cell death. The positive control cisplatin showed  $60\% \pm 1\%$  cell death under the same conditions. Results of this study are statistically averaged after three independent studies as well.

Other pertinent data of biological activity studies can be found in Jessica Ratcliff MS thesis located in the Meyer Library of Missouri State University.

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Work of Jessica Ratcliff in my research group has resulted in 3 presentations at the regional and national meetings of the American Chemical Society, and international conference:

1. Cheadle, C.; Gerasimchuk, N.; Kolesnichenko, V.; Ratcliff, J. "Nickel triad complexes of the amide-cyanoximes containing N-morpholyl-, N-piperidine- and bis-N-piperazine groups." Proceedings of 42<sup>nd</sup> Midwest Regional Meeting of the ACS, p.138; Kansas City, MO, 2007.
2. Durham, P., Sedivy, D., Keck, M., Ratcliff, J., Gerasimchuk, N.N. "New cytotoxic bivalent Pd and Pt cyanoximates." Inorganic chemistry section, poster presentation (733). Fall 232 ACS Meeting, September 7-11<sup>th</sup>, 2006, San Francisco, CA.

3. Durham, P., Sedivy, D., Keck, M., Ratcliff, J., Gerasimchuk, N.N. "New cytotoxic bivalent Pd and Pt cyanoximates." P. 314 in Proceedings of the ICC-37 Posters Abstracts book; Cape Town, August 13 - 18<sup>th</sup> 2006, South Africa.

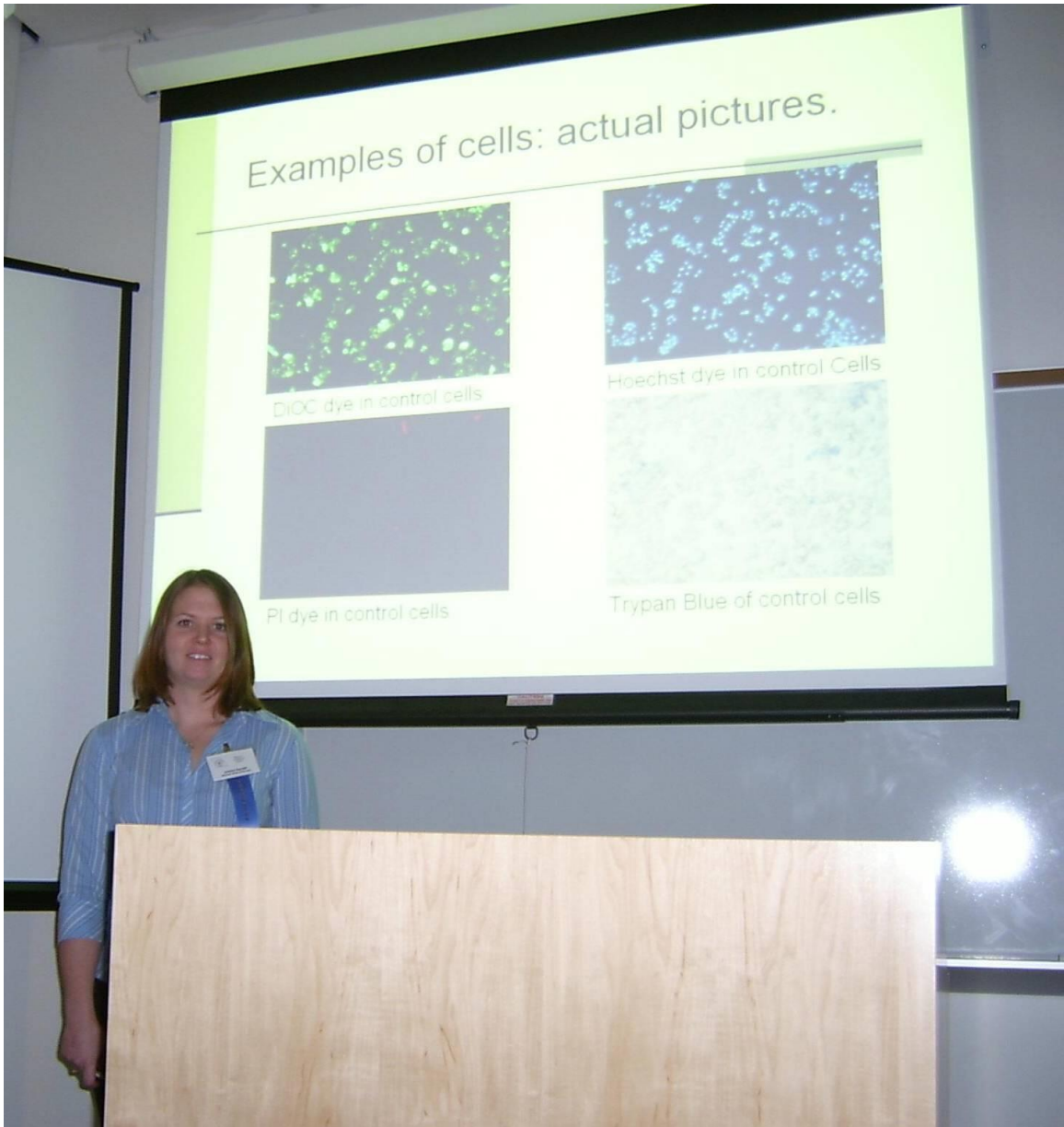
Three major peer-reviewed publications resulted from Jessica's work in my research group:

- 1) Cheadle, C.; Ratcliff, J.; Berezin, M.; Pal'shin, V.; Nemykin, V.N.; Gerasimchuk, N. "Shortwave infrared luminescent Pt-nanowires: a mechanistic study of emission in solution and in the solid state". *Dalton Transactions*, **2017**, 46(39), 13562-13581.
- 2) Ratcliff, J.; Kuduk-Jaworska, J.; Chojnacki, H.; Nemykin, V.N.; Gerasimchuk, N. "Part 1: Experimental and theoretical studies of 2-cyano-2-isonitroso-N-piperidynylacetamide (HPiPCO), 2-cyano-2-isonitroso-N-morpholylacetamide (HMCO) and their Pt- and Pd-complexes." *Inorganica Chimica Acta*. **2012**, 385, p.1-11.
- 3) Ratcliff, J.; Durham, P.; Keck, M.; Mokhir, A.; Gerasimchuk, N. "Part 2: In vitro Cytotoxicity Studies of Two ML<sub>2</sub> Complexes (M = Pd, Pt; L = 2-cyano-2-isonitroso-N-morpholylacetamide, HMCO)." *Inorganica Chimica Acta*. **2012**, 385, p.11-20.

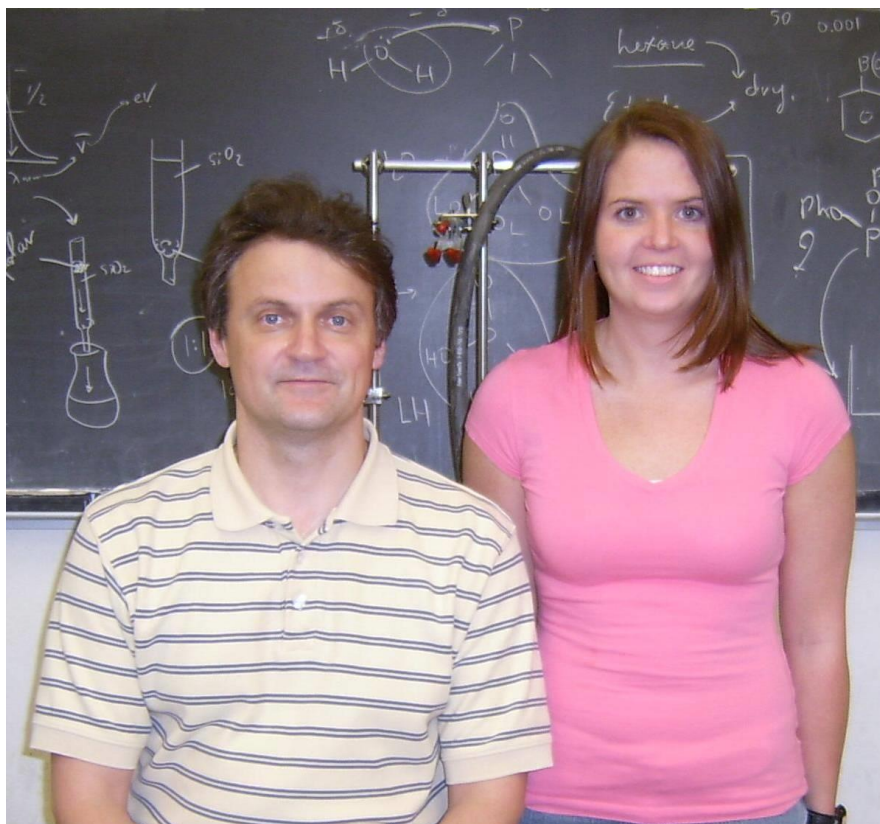




*Graduation DAY!*



Presentation at the Missouri Academy of Sciences Meeting in Kirksville, MO (2005)



In the research laboratory.



A photo during trip to Missouri Academy of Sciences meeting.