**Supplemental information and data**

1. **Supplementary figures**

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**Figure S1. Orthogonal View of two representative cell images.** An orthogonal view of the overlay of the DAPI (blue) and Zinc Oxide SMPs (orange) stain pictures. The big picture shows the xy axis view, the vertical bar image shows the yz axis view, and the horizontal bar image on the bottom shows the xz axis view.

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**Figure S2. Cell internalized more Rods than Flowers.** Significantly more internalized particles were observed with Rods than Flowers, as quantified by fluorescence area ratio. \*: *p* < 0.05

A picture containing diagram

Description automatically generated

**Figure S3. Cytotoxicity representative images.** ZnO SMPs were more toxic to the cancer cell line (GSC33) than the non-cancerous ones (L929). Rods were more toxic than the Flowers. Green: live cells; Red: dead cells (n=3).

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**Figure S4. Wound healing representative images.** ZnO SMP inhibited cell migration of the cancer cell line (GSC33) more effectively than the non-cancerous ones (L929). Rods were more efficient than the Flowers. Yellow dotted lines separate blank areas and cells (n=3).

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**Figure S5. The degradation of ZnO NPs follows the integrated rate law of the Zeroth order.** The degradation profiles did not fit well with the First-order and the Second-order, judging by the resulting poor R-square values (< 0.85). However, fitting of the Zeroth-order resulted in a trustable R-square value (> 0.91).

1. **Supplementary tables**

**Table S1. Standard Error for Zeta-potential**

|  |  |  |
| --- | --- | --- |
| **Standard Error** | **Flower** | **Rod** |
| **pH5.0** | 0.46205 | 0.40318 |
| **pH6.0** | 0.365813 | 0.633589 |
| **pH7.0** | 0.321464 | 0.688819 |

**Table S2. Genes’ primer sequence**

|  |  |  |  |
| --- | --- | --- | --- |
| **Genes** | **Primer sequence (5’-3’)** | **Product size** | **GenBank Accession** |
| **Ki-67** | F: CATCAAGGAACAGCCTCAAC  R: GTTGACTTCGGCTGATAGAC | 257 bp | NM\_001145966.2 |
| **PYK2** | F: GAGACCTACCGCTGTGAAC  R: CTGCTAGGGATGAGGTTTTG | 232 bp | NM\_173174.3 |
| **ATX** | F: TATGCTTCGGAAAGAAATGGAG  R: ATGTTCAATGTCACGCACCCT | 327 bp | NM\_001330600.2 |
| **β-actin** | F: AGCGGGAAATCGTGCGTG  R: CAGGGTACATGGTGGTGCC | 309 bp | NM\_001083538.3 |

**3. The details of Welch’s t-test**

Let be the LogIC50 for the population, and we would like to know whether for any two populations . The true value of cannot be known, which instead must be estimated from the experiment by an estimator denoted by . The difference of and is assessed by a statistical test of the null hypothesis

against the alternative

based on the values of and .

Under a reasonable assumption of normality of the population (data), has the normal distribution with mean and variance . If and are computed independently, which is true in our case, also has a normal distribution, with mean and variance . With proper standardization, we have

Under the null hypothesis, we have and consequently

Thus, significant tests can be performed based on the standard normal distribution.

In practice, however, the true value of is usually not known and estimated by the sample variance . After replacing by , the above statistic will no longer follow the standard normal distribution due to the extra uncertainty.If we assume , the common variance can be estimated by a pooled sample variance defined as

where and are the number of data points in the experiments for populations and , respectively. The new test statistic replacing with follows the student’s t-distribution with the degree of freedom (DF) equal to , i.e.

This is essentially a slight variation of the two-sample t-test with equal variances. When the two populations do not have equal variances, which is in our case, the idea of pooling makes no more sense. Instead, one needs to replace with and with , respectively. Thus, the test statistic is defined as

The exact distribution of under depends on and cannot be obtained. Nevertheless, for moderate to large sample sizes, it can be well approximated by the t distribution with DF

rounded down to the nearest integer, where and are degrees of freedom for and , and . This test is known as Welch’s t-test for unequal variances [1][2]. In order for the approximation to be good and the test to be accurate, both and must be at least 5.

**Welch’s t-test Matlab code:** [t,p\_val,df] = welch\_test(x1,x2,SE1,SE2,df1,df2)

**References**

1 Welch BL. On the Comparison of Several Mean Values: An Alternative Approach. *Biometrika.* 38(3/4), 330-336 (1951).

2 Welch BL. The generalisation of student’s problems when several different population variances are involved. *Biometrika.* 34(1-2), 28-35 (1947).