Using virus genes and proteins to fight influenza

使用病毒基因和蛋白對抗流感

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Dual-functional peptide with defective interfering genes effectively protects mice against avian and seasonal influenza

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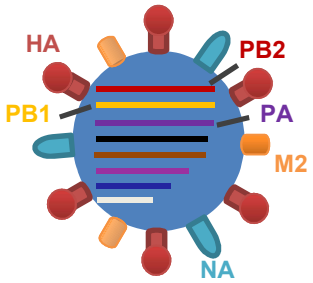
The current status of anti-influenza drugs
抗流感藥物的現狀

- Presently available anti-influenza drugs: zanamivir (Relenza) and oseltamivir (Tamiflu)
  目前抗流感病毒的藥物包括扎那米韋（樂感清）和特敏福

- They are effective only if given within 48 hours of symptom onset; and resistance can develop rapidly.
  這些藥物治療流感的效果有限，且易產生耐藥性

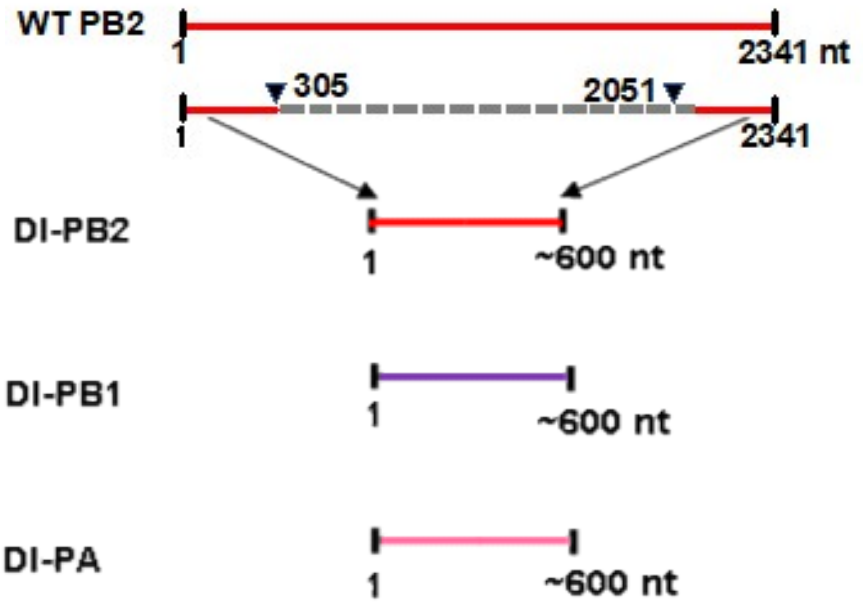
- Human isolates of A(H1N1), A(H3N2), A (H5N1), and A(H7N9) resistant to neuraminidase inhibitors have been found.
  人類流感(H1N1, H3N2)和禽流感(H5N1,H7N9) 已發現耐藥病毒株



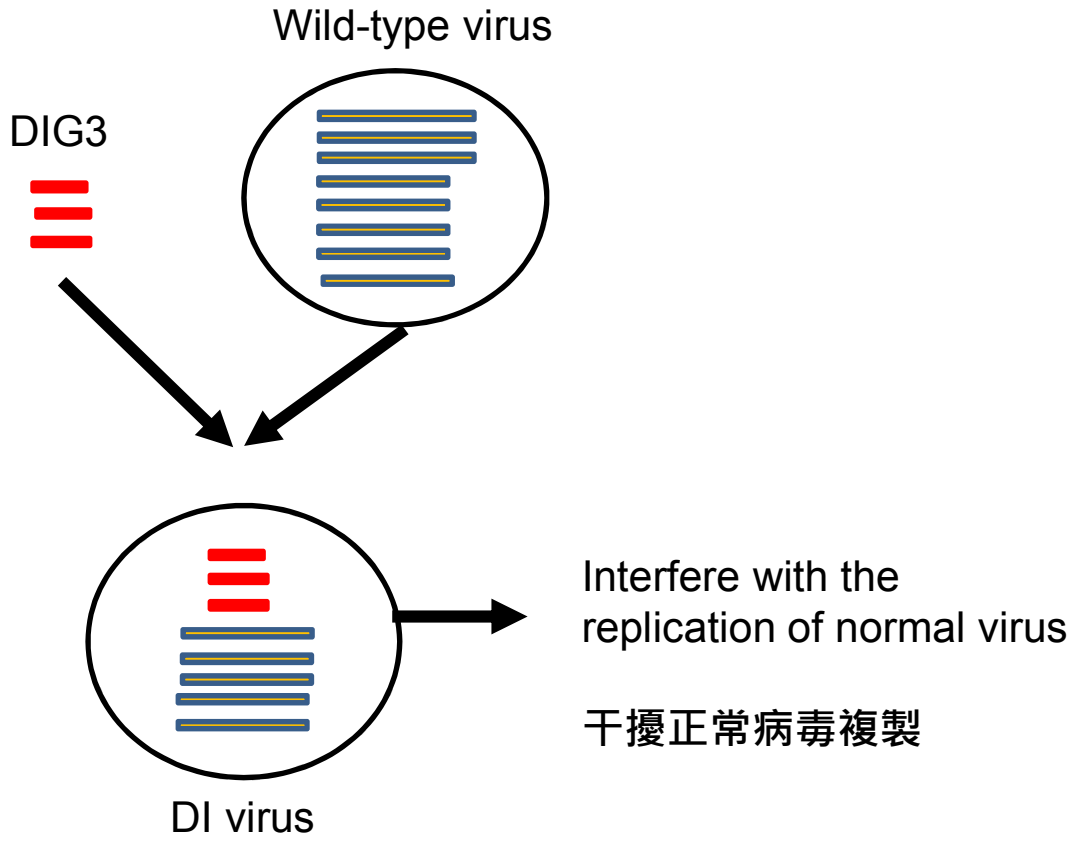
WTV野生型病毒

Design of new antiviral DIG3

以毒攻毒：使用病毒基因 (DIG3) 對抗流感病毒



DIG3 reassorts with normal virus genes, generating defective interfering virus
缺陷干擾基因與正常的基因洗牌，產生缺陷干擾病毒

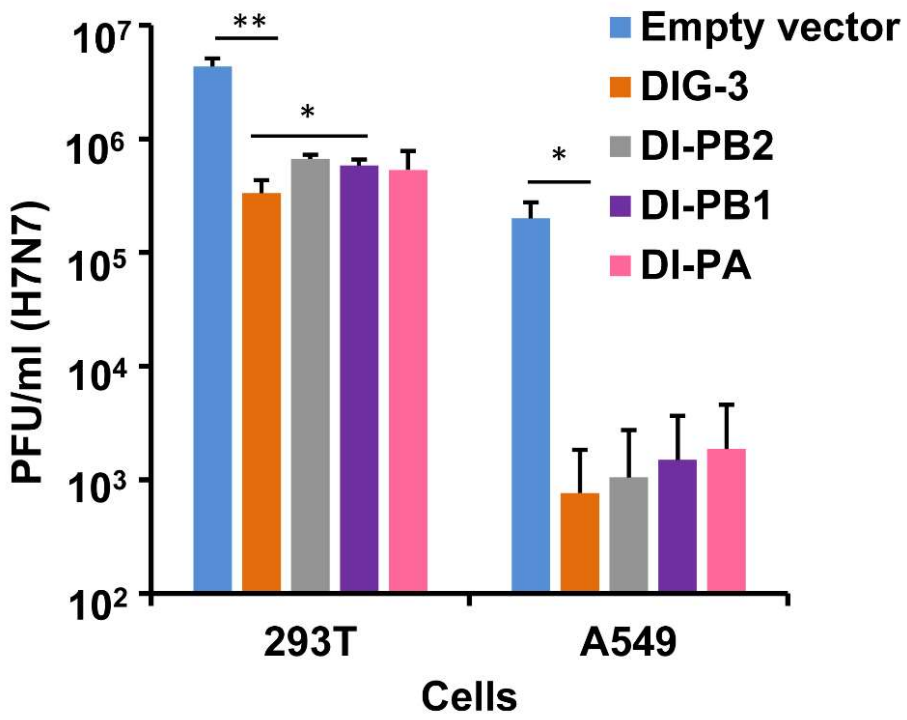


Advantages of using DIG3
DIG3的優點

1. includes the conserved sequences for influenza virus packaging
2. **low possibility** to induce resistance
3. **broad** anti-influenza activity
4. no new live virus generated

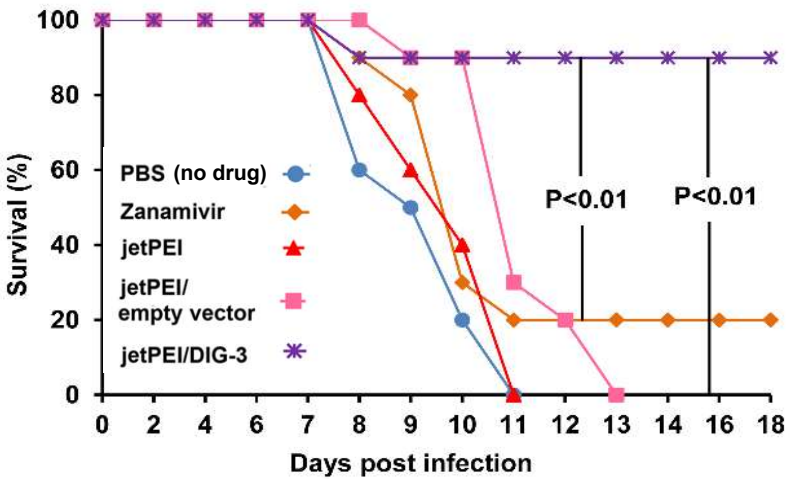
1. 具備重要的流感病毒保守序列 (賴以包裝病毒顆粒的基本原件)
2. 不容易產生耐藥性
3. 具備廣譜抗流感病毒活性
4. 不會產生新的活病毒

DIG3 inhibits virus replication of H7N7 in cells
DIG-3抑制細胞中的禽流感H7N7病毒複製

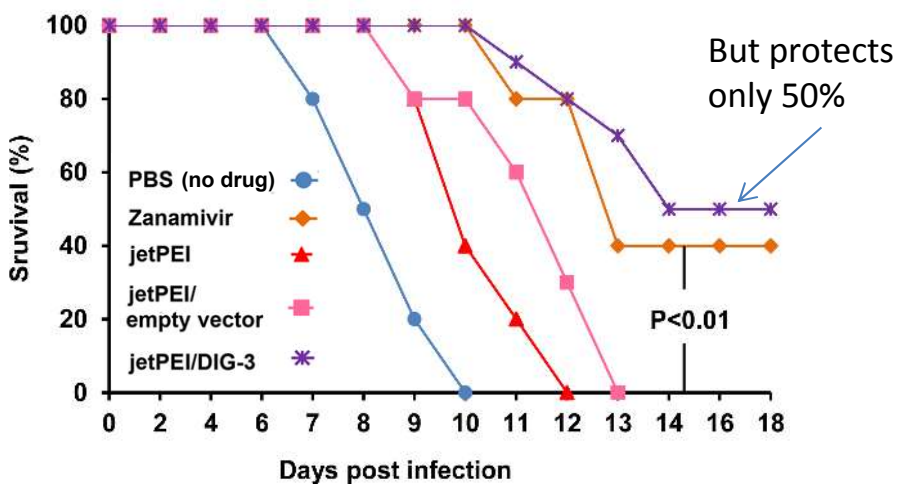


DIG3 protects mice from H7N7 infection
DIG3 預防和治療H7N7流感

a. Prophylactic protection on mice
（預防）



b. Therapeutic protection on mice
（治療）



Discovery of dual-functional protein (TAT-P1) for DIG delivery
研發雙功能基因載體

HIV-TAT: can deliver DNA into cell
HIV-TAT蛋白將病毒缺陷干擾基因導入細胞內

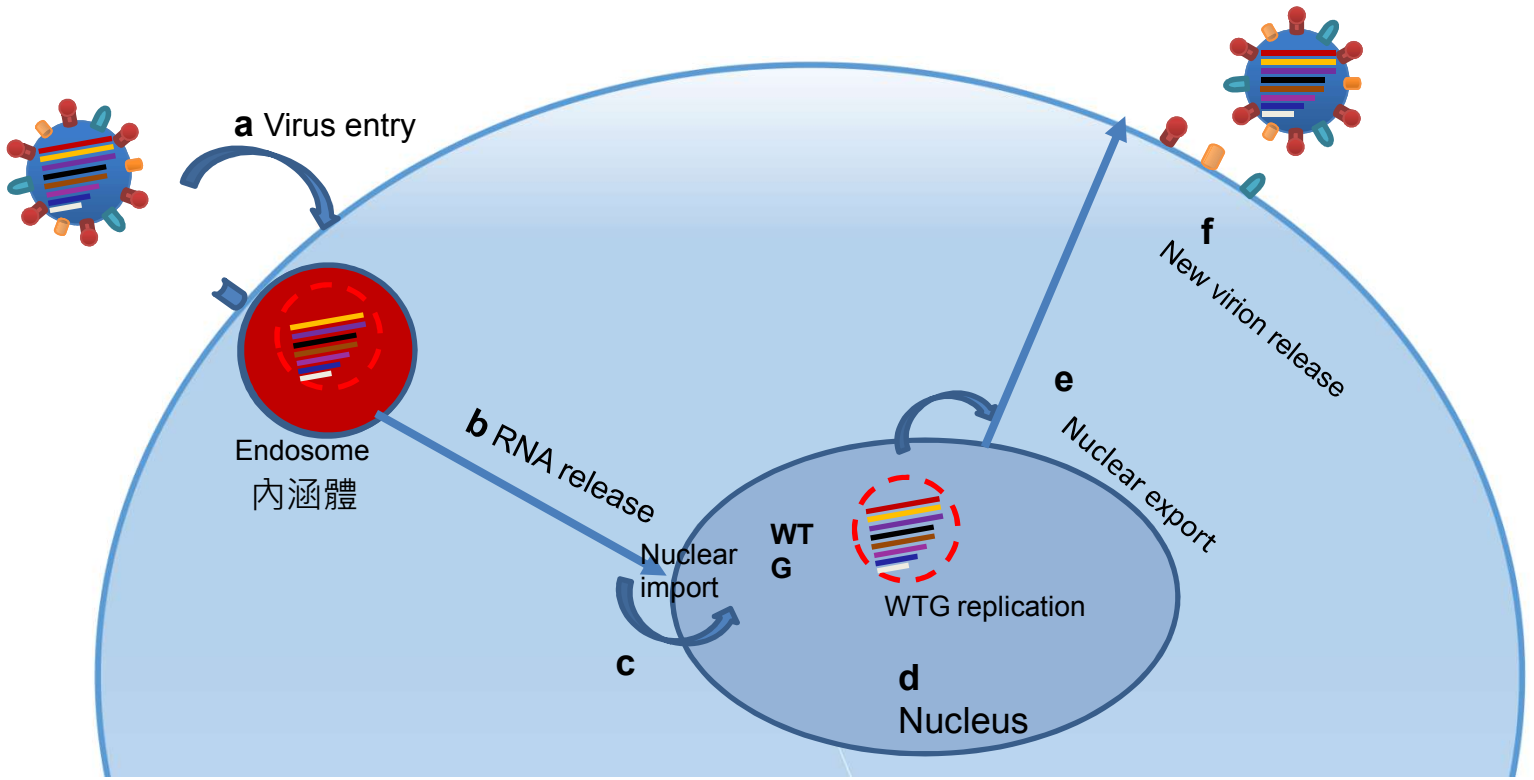
P1: protein which inhibits pH decrease in endosome of cells to reduce virus entry.
蛋白P1能夠有效阻止細胞內涵體的pH值降低，從而抑制病毒進入細胞質內

TAT-P1: Dual-function for DIG delivery and inhibit virus entry into cytoplasm
蛋白TAT-P1具有雙重功能

Life cycle of normal influenza virus infection
流感病毒感染細胞的病毒複製週期

: pH > 6 in endosome

: pH < 6 in endosome

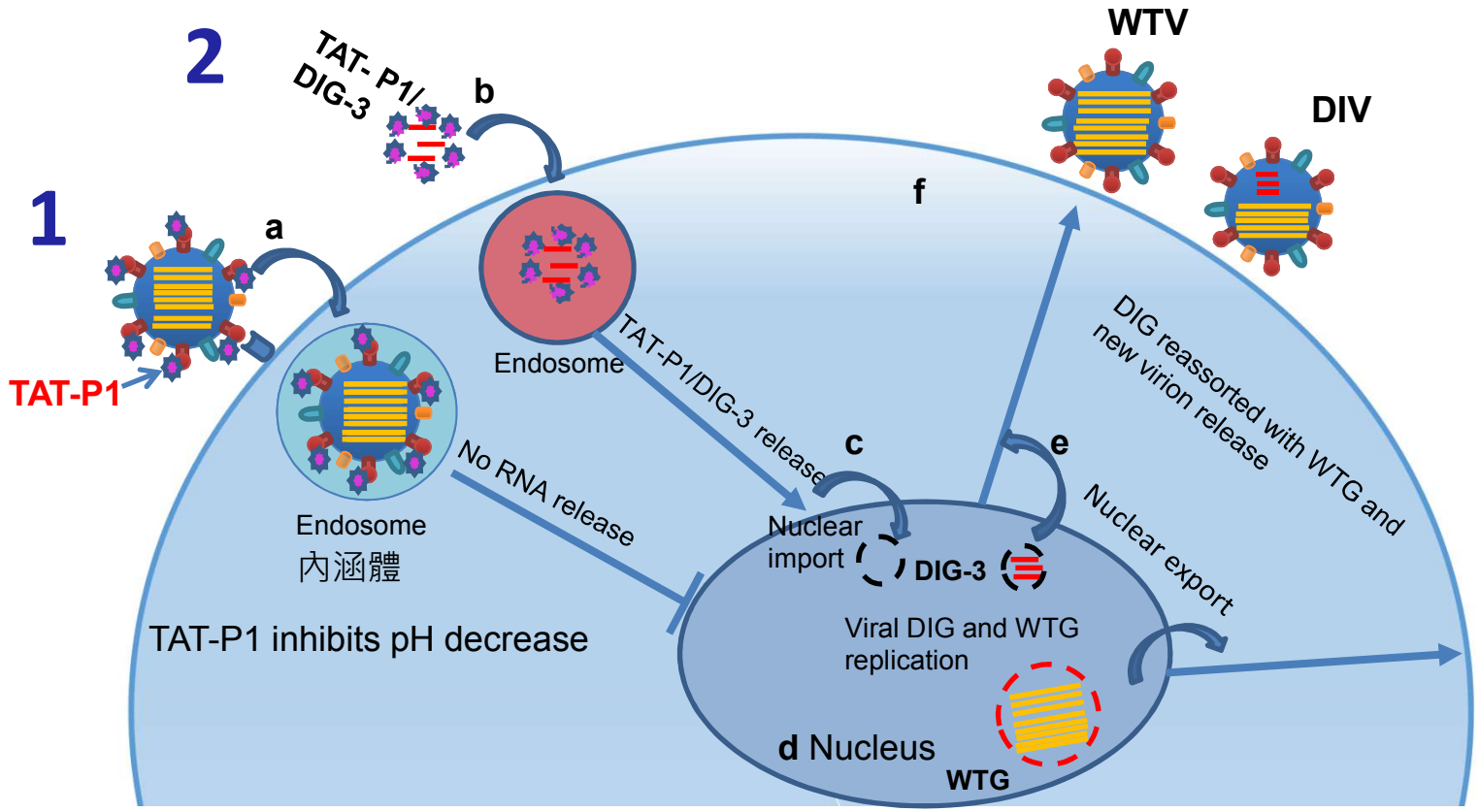


Two steps of virus inhibition by TAT-P1/DIG3 in one life cycle
雙重抗病毒機制

: pH < 7 in endosome

: pH > 6 in endosome

WTV: wild type virus
WTG: wild type gene
DIV: DI virus



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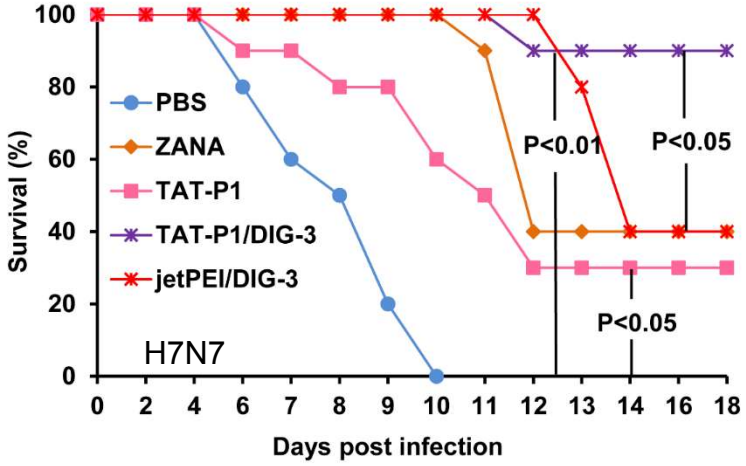
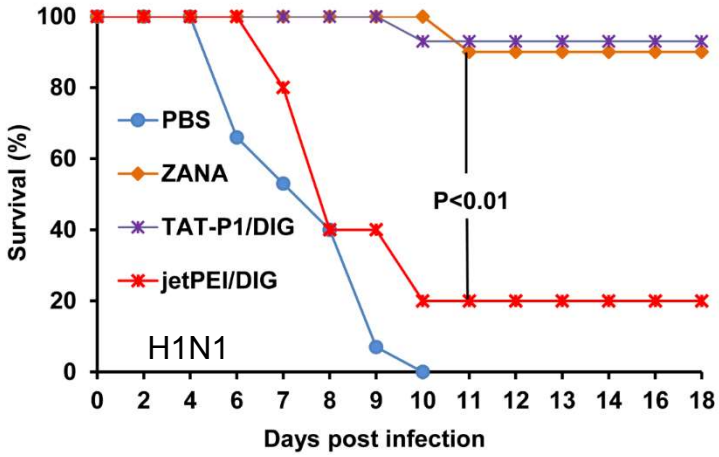
TAT-P1/DIG3 protected mice from H7N7 and H1N1 infection
TAT-P1/DIG3有效治療H7N7和 H1N1感染

a. Survival of H7N7-infected mice: TAT-P1/DIG3 **better** than zanamivir
TAT-P1/DIG3比扎那米韋更好

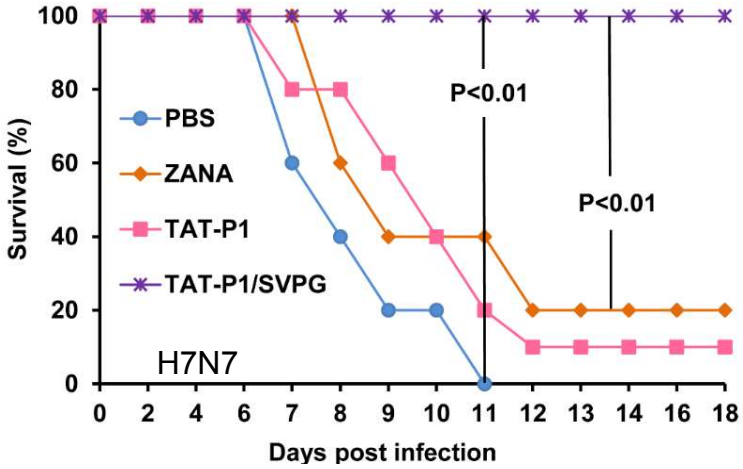


b. Survival of H1N1-infected mice: TAT-P1/DIG3 is similar to zanamivir
TAT-P1/DIG3 和扎那米韋有相似的效果

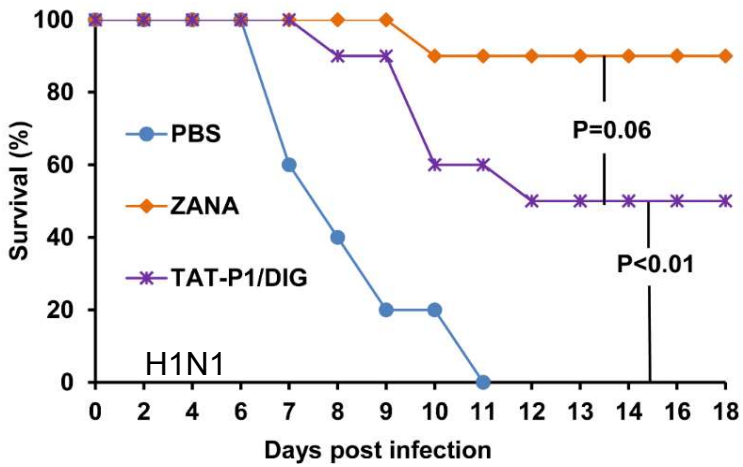


TAT-P1/DIG3 protects mice as prophylaxis
TAT-P1/DIG3有效預防H7N7和 H1N1感染

a. Survival of H7N7-infected mice: TAT-P1/DIG3 **better** than zanamivir
TAT-P1/DIG3比扎那米韋有更好的預防效果



b. Survival of H1N1-infected mice: not better than zanamivir for protecting mice.
TAT-P1/DIG3有預防保護作用，但不及扎那米韋



Significance of the study
研究意義

1. **First time** that defective interfering genes shown to protect flu-virus-infected mice
2. **Major advantages** of using defective interfering genes (DIG): broad spectrum antiviral activity, low risk of developing resistance and no life virus generation.
3. **First gene delivery system with** antiviral activity against influenza virus in mice.
4. **Important implications** for future treatment of influenza and other virus infections.

1. 缺陷干擾基因（DIG3）第一次被證實在小鼠體內具有抗流感作用。
2. 主要優點是：用缺陷干擾基因治療流感具有廣譜抗病毒活性，不容易產生耐藥病毒，不會產生新的病毒而危害人類生命。
3. 研究團隊設計出新的基因載體TAT-P1，同時具備抗流感病毒活性，並成功將這種方法應用於動物模型治療流感。
4. 研究對將來流感以及其他病毒感染的治療提供了重要的方法和科學依據。

Thank you