Lecture 13: Designing nanomedical systems (NMS) for in-vivo use

13.1 Bringing in-vivo considerations into NMS design
    13.1.1 the in-vitro to ex-vivo to in-vivo paradigm
            13.1.1.1 In-vitro - importance of choosing suitable cell lines
            13.1.1.2 adding the complexity of in-vivo background while keeping
                    the simplicity of in-vitro
            13.1.1.3 all the complexity of ex-vivo plus the "active" components of
                    a real animal
    13.1.2   In-vivo systems are open, "active" systems with multiple layers of complexity
            13.1.2.1 In-vitro and ex-vivo are mostly "closed" systems, but not absolutely
            13.1.2.2 What is an "open" system?
            13.1.2.3 Attempts to isolate open systems
     13.1.3 Layers of complexity of in-vivo systems
            13.1.3.1 Human cells in nude mice – a mixture of in-vitro and in-vivo
            13.1.3.2 "Model" small animal systems
            13.1.3.3 better model larger animal systems

13.2 Circulation time and biodistribution
    13.2.1 factors affecting circulation time
            13.2.1.1 size/shape
            13.2.1.2 "stealth layer" coating
            13.2.1.3 zeta potential in-vivo in varying environments
            13.2.1.4 filtration and excretion
            13.2.1.5 dose/targeting
    13.2.2. where do the NMS go in-vivo?
            13.2.2.1 checking the obvious organs (liver, spleen, kidney, blood…)
            13.2.2.2 finding NMS in tissues and organs
                    13.2.2.2.1 in-vivo
                    13.2.2.2.2 within dissected tissue sections
                    13.2.2.2.3 in blood (ex-vivo versus in-vivo flow cytometry)
                    13.2.2.2.4. what is excreted?
    13.2.3 Circulation time and dose optimization
            13.2.3.1 measure drug concentration over time
            13.2.3.2 is there an optimal drug dose?

13.4 In-vivo targeting and mistargeting
    13.4.1 mode of administration (intravenous, oral, intra-tumor…)
    13.4.2 how can we assess targeting in-vivo? (MRI, fluorescence, …)
    13.4.3 a rare-cell targeting problem
    13.4.4 consequences of mistargeting
    13.4.5 balancing dosing, therapeutic efficacy, and consequences of mistargeting

13.5 Evaluating therapeutic efficacy in-vivo
    13.5.1 advantages of non-invasive measurements
    13.5.2 measures of tumor load/shrinkage (tumor size, weight,..)

13.5.3 other measures of disease effects
      13.5.3.1 direct measurement of restoration of lost or compromised functions
      13.5.3.2 indirect measures of disease effects (e.g. behavior, weight gain/loss, .)
13.5.4 Some examples of in-vivo work with NMS

13.6 Summary
  13.6.1 Choosing an appropriate animal model and getting it approved takes time!
  13.6.2 Animal experiments are expensive and time-consuming
  13.6.3 Performing in-vivo measurements of drug delivery and therapeutic efficacy are
        more challenging and expensive than in-vitro or ex-vivo work!
  13.6.4 But ultimately you must show that the NMS works in-vivo

References

Bhirde, A.A., Patel, V., Gavard, J., Zhang, G., Sousa, A.A., Masedunskas, A., Leapman, R.D., Weigert, R., Gutkind, J.S., Rusling, J.F. Targeted Killing of Cancer Cells in Vivo and in Vitro with EGF-Directed Carbon Nanotube-Based Drug Delivery. ACS Nano 3(2) 307-316 (2009).

Cartier, R., Kaufner, L., Paulke, B.R., Wustneck, R., Pietschmann, S., Michel, R., Bruhn, H., Pison, U. Latex nanoparticles for multimodal imaging and detection in vivo. Nanotechnology 18:195102 – 195113 (2007).

Chenga, J., Teply, B.A., Sherifia, I., Sunga, J., Luthera, G., Gua, F.X., Levy-Nissenbauma, E., Radovic-Morenob, A.F., Langer, R., Farokhzad, O.C.
Formulation of functionalized PLGA–PEG nanoparticles for in vivo targeted drug delivery. Biomaterials 28: 869–876 (2007).

Farokhzad, O.C., Cheng, J., Teply, B.A., Sherifi, I., Jon, S., Kantoff, P.W., Richie, J.P., Langer, R. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. PNAS 103(6): 6313–6320 (2006).

Hou, C-H, Hou, S-M, Hsueh, Y-S, Lin, J., Wu, H-C, Lin, F-H The in vivo performance of biomagnetic hydroxyapatite nanoparticles in cancer hyperthermia therapy Biomaterials 30: 3956–3960 (2009).