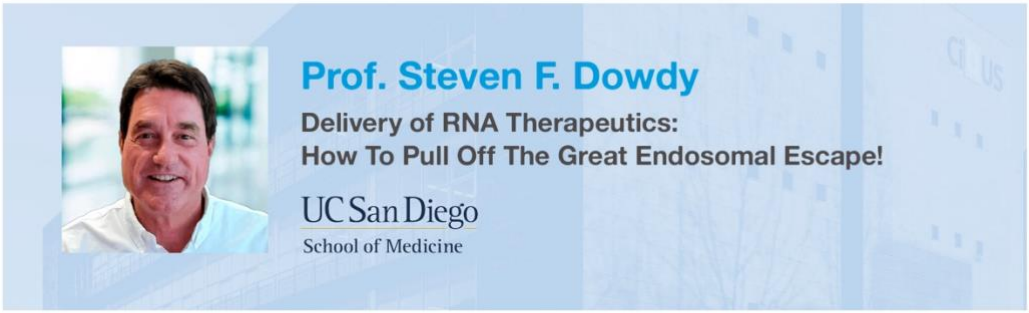
CiQUS Lecture



FONDO EUROPEO DE DESENVOLVEMENTO REXIONAL
PO FEDER Galicia 2014-202 - *Unha maneira de facer Europa*

Friday, October 27, 2023
12:30 pm - CiQUS Seminar Room

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Abstract:

RNA therapeutics have shown great promise in treating a limited number of human diseases in select permissive tissues. Unfortunately, other indications, such as cancer and viral pandemics, remain recalcitrant to treatment by RNA therapeutics. Unlike small molecule therapeutics that are designed to passively diffuse across the cell membrane's lipid bilayer, RNA therapeutics are too large, too charged and/or too hydrophilic to cross this billion year old evolutionary defense. Instead, RNA therapeutics are taken up by various forms of endocytosis. However, endosomes are also composed of a lipid bilayer that prevents escape of RNA therapeutics into the cytoplasm. Indeed, only ~1% or less of endocytosed RNA therapeutics escape from the endosome, leaving >99% entrapped inside of endosomes. Unfortunately, there are currently no acceptable, non-toxic solutions to solve the endosomal escape problem. Given the magnitude of impact that solving the endosomal escape problem would have on the entire RNA therapeutics field (and perhaps others), if it was easy, research over the last 40+ years would have solved it. Moreover, the more we work on endosomal escape, the greater the appreciation I have for how difficult it will be to successfully overcome in a non-toxic, clinically acceptable manner. In our way of thinking of potential solutions, a successful endosomal escape domain (EED) should incorporate the following parameters:

1. Ten-fold or greater enhanced endosomal escape in the absence of cytotoxicity,
2. Covalently linked to RNA therapeutic, hydrophilic and inert in plasma, but selectively activated inside of endosomes to expose hydrophobicity and/or cationic charge,
3. Causes a localized endosomal lipid bilayer disruption, not endosomal rupture,
4. Biophysical properties do not interfere with targeting domains.

While this sounds straightforward and achievable, to date, developing EEDs capable of fulfilling all four parameters has remained elusive. Indeed, many, if not most, of the approaches that dramatically enhance endosomal escape appear to result in endosomal rupture, which even if

engineered to be highly controllable, will likely result in clinically unacceptable toxicity. Consequently, before RNA therapeutics can be used to treat widespread human disease, the rate-limiting delivery problem of endosomal escape must be solved. Our approach to address the endosomal escape problem has been to chemically synthesize novel EEDs that are biomimetics of the mechanism that enveloped viruses use to solve their endosomal escape.

Biosketch:

Steven F. Dowdy, Ph.D., is a Professor of Cellular & Molecular Medicine at UCSD School of Medicine. He received his PhD in Molecular Genetics from the University of California Irvine with Prof. Eric Stanbridge and was a postdoctoral fellow with Prof. Bob Weinberg at the Whitehead Institute, MIT.

In 1994, Dr. Dowdy became an Investigator of the Howard Hughes Medical Institute and an Assistant Professor at Washington University School of Medicine. He moved his lab to UCSD in 2001. His early research focused on understanding the molecular basis of G1 cell cycle deregulation during oncogenesis by RB, p16 and cyclin:Cdk complexes, determining that cyclin D:Cdk4 complexes activated RB by mono-phosphorylation. Concurrently, another line of his research in his lab focused on the intracellular delivery of macromolecular therapeutics, including siRNAs, ASOs, peptides and proteins, to ultimately treat cancer.

His work over the last 10+ years has focused on developing new chemistry to tackle the rate-limiting endosomal escape problem that plagues intracellular delivery of all macromolecular therapeutics, especially RNAs.

Dr. Dowdy has been advising biotech and pharmaceutical companies for 35 years, currently sits on five biotech science advisory boards and is co-founder of Clear Skies Bio, which is focused on RNA delivery. He was an elected board member of the Oligonucleotide Therapeutics Society (OTS) (2015-2021) and sits on the OTS science advisory board.