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Modeling cellular adsorption

Therapeutic agents including chemical compounds and aptamers that target to act intracellularly offer no clues during their design or discovery phases on their cellular pathways so end up causing cytotoxicity. A standard drug delivery template is due for specific agent. An agent specific probability distribution function (PDF) is developed using condensed matter physics and considering information from the biophysical properties of interaction sites, the pseudo barriers, transient or permanent openings on the cell surface and importantly the membrane hydrophobic barriers.

The PDF, p (r,r';t,t'), is a conditional probability of finding the particle at spatial position r at time t on cell surface relative to at another position r' at time t' on the same or other side of the cell surface. The PDF is related to the dynamic correlation or interaction of the particle with cell surface structures. Thus even the particle is temporarily or permanently trapped at a distorted cell surface, p (r,r';t,t') will shed the light to determine the probability of observing such a trap. And this information will lead to determining the probability of observing membrane permeabilization. The PDF, p (r,r';t,t'), is drug (aptamer or any other agents) specific and relying heavily on cell surface environment. Numerical computation on the complex probability function and *in vitro* demonstration are used to quantitatively predict these PDFs on the target site and off-target sites. Information of these two PDFs will be fed back to designing phase to reengineer the agents to have higher chances to penetrate membrane and interact with intracellular targets. The reengineered agents will thus be ready for cell studies.

Three specific aspects we address in MDT Canada premise using the validated and published method:
1. Membrane adsorption test and quantification
2. Membrane permeation test and quantification
3. Cellular target binding test and quantification

Why probability distribution function?

- The likelihood of drugs reaching target of interests
- Mechanisms for drugs trapped in intermediate pathway and encountered off target binding
- Strategy to reengineering drug properties to increase membrane permeability

Our technology

	Objective	Result
Method-*in silico*	Algorithm that incorporates condensed matter theory of interactions to evaluate PDFs of agent of interests	Probability analysis
Method-*in vitro*	Liposome binding assay for drug	Pathway barrier test
	Electrophysiology record across agent induced modulated bilayer barrier	Ways to remove barriers
	Target/protein structure binding assay	Drug deliverability

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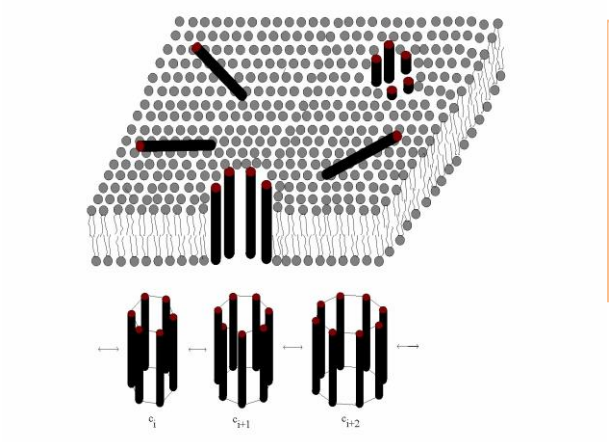
Comparison between our technology and conventional approach

	Our technology		Conventional approach
	In silico method	*In vitro* method	
Approaches	Two methods: (i) Statistical mechanical approach to define drug's probability distribution function (PDF) (ii) Computer programming based calculation of drug's PDFs at various drug targets, off-targets and barriers.	Novel and controlled binding assay, induced barrier transport mechanisms and known drug pathway delivery	No *in silico* method available. Random incubation of drugs across barriers and natural diffusion at a cost of high cytotoxicity.
Drug reengineer	Feedback of information on PDF and barrier delivery to drug redesign phase.		No method available
Target	Time	Time	Time
Membrane barrier	1 week for 1 drug/agent	1 week for 1 drug/agent	No plan available
Any structure/protein	2 weeks for 1 drug/agent	2 weeks for 1 drug/agent	No plan available



Example of modeling channels formed by one of antimicrobial peptides, alamethicin. Each black rod represents monomers on a "barrel-stave" pore. Transistions between different alamethicin conductance pores by addition/release of monomer(s) from/to the surrounding space are shown in the lower panel.

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Service	What do you get?
Membrane Service-*In silico*	Membrane permeation. The PDF for a drug crossing cell surfaces based on *in silico* method will be determined. Given this PDF, membrane permeability for this drug will be estimated. Service includes basic report on derivation of PDF and numerical analysis.
Membrane Service- *In vitro*	Membrane permeation. Two services: (i) Liposome binding assay-membrane adsorption probability addressing the ralative value of PDF in cell membrane. (ii) Lipid bilayer membrane release/diffusion probability addressing the relative values of PDF beyond cell membrane (intracellular region). Service includes basic report on assay techniques and data analysis.
Protein Service-*In silico*	Protein binding. The PDF of a drug bind to a protein target/binding site based on *in silico* computation will be determined. Service includes basic report on derivation of PDF and numerical analysis.
Protein Service-*In vitro*	Protein binding. The values of PDF for a drug at a protein binding site based on *in vitro* binding assay. Service includes basic report on assay techniques and data analysis.
Complete	Any combination from above 4 options.

Why MDT Canada Inc.?

We have a unique platform combining theoretical, computational and experimental expertise and techniques to provide services and fulfil your needs through consultations.

Please send all of your inquiries to contact@mdtcanada.ca

We will be happy to set up a meeting with you to discuss your needs. A quotation will be made considering services you choose.

When you can utilize informatics why doing random tests!