

mRNA

at the ballet



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# ACT I: THE BALLET

## *The first performance*

The ballet is over and it's time for the final curtain call. The prima ballerina and the male principal dancer wait behind the curtain. Let's call her Anna, and let's call him Mikhail. The curtain rises and they stride triumphantly to center stage. Anna stands to Mikhail's right, holding his right hand.

The audience erupts in applause, with shouts of "Bravo!" and "Brava!" Mikhail bows, left arm uplifted, thighs as big as tree trunks, and smiling broadly. Anna curtsies, her enormous puffy tutu bobbing ever so slightly, her lovely face aglow in the spotlight.

The applause goes on and on. To mix things up, Anna twirls to face Mikhail, taking his left hand while still holding his right. She then releases his right hand, completing her turn. She's now standing to Mikhail's left, holding his left hand. They repeat this move several times, right to left, left to right.

The audience loves it and their applause becomes even louder. They begin to chant "Anna! Anna! Anna!" for the prima ballerina. Releasing Mikhail's hand, she moves downstage, past the proscenium arch and onto the apron. The audience rises to its feet as one, chanting and applauding ever more loudly. Anna is showered with applause and bouquets of flowers as she bows and curtsies and waves to the crowd.

Offstage, the ballet mistress is fuming silently. Before the performance, she gave Anna and Mikhail strict instructions to stay in position during the final curtain: holding hands, with Anna to Mikhail's right. And they were ignoring her, rejecting her authority. Her black-clad figure blends into the shadows, interrupted by the occasional glint of light from her glasses and her graying hair, which has been pulled back into a too-tight bun. She taps her cane quietly, rhythmically, in irritation.



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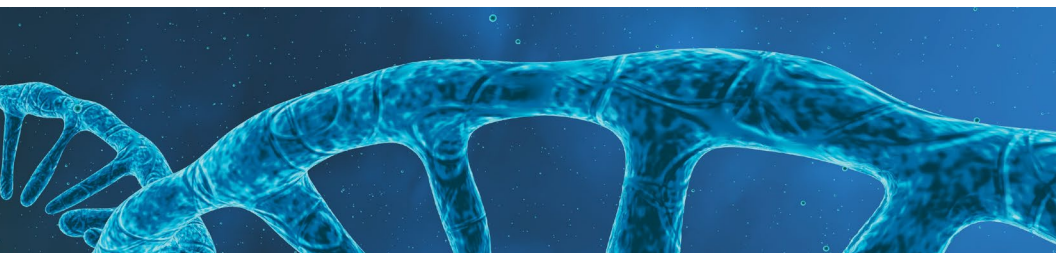
## *The second performance*

The following night, there is another performance, even more exquisite and energetic than the night before. The ballet mistress is determined that this time, Anna and Mikhail will obey her instructions. Before the final curtain rises, stagehands bring out two chairs and place them behind Anna and Mikhail. They're the kind of stackable chairs that you find in banquet halls and meeting rooms, with cheap plastic bucket seats. The seats are coated with superglue. Anna and Mikhail are pushed down, gently, so they're sitting in the chairs. As the curtain rises, the stagehands carry them to center stage. They're holding hands, Anna to Mikhail's right.

The audience is confused and momentarily silent. But then there is whispered realization that the dancers must be tired, and surely they're sitting down because they're exhausted. Applause erupts, amid "Bravo! Brava!" as before. Offstage, the ballet mistress smiles and gloats.

But Anna is determined to have her moment. Reaching down, she grabs the sides of her chair and begins to scoot toward Mikhail's left side. Ka-chunk, ka-chunk, ka-chunk. Ka-chunkity-chunk. A brief pause to smile and wave graciously to the audience, and then ka-chunk, ka-chunk until she reaches Mikhail's left side. She takes his left hand, amid wild applause. Emboldened, Anna then releases Mikhail's hand and ka-chunk, ka-chunks her way downstage, where she is again showered with flowers and adulation. Her performance has been a triumph, and in more ways than one.

Offstage, the ballet mistress is livid. Her screams of rage are swallowed up in the applause. Her glasses are askew and her hair has come undone. Her cane falls to the floor with a loud clatter, but no one hears it. She doesn't know quite what to do, but she's more determined than ever that this appalling spectacle will not be repeated.



# ACT I: THE BALLET

## *The third Performance*

On the third night, there is another performance, every bit as beautiful as the other two. Moments before the final curtain call, the ballet mistress handcuffs Anna and Mikhail together, joining his right wrist to her left. The ballet mistress then locks the handcuffs and pockets the key, retreating offstage into the shadows.

Center stage, Anna and Mikhail bow and curtsy as usual. Anna takes Mikhail's left hand and begins to pivot toward his left side. But she can't complete the turn—the handcuffs make it impossible for her to release Mikhail's right hand. Anna then begins her walk downstage to be strewn with flowers. But of course, Mikhail can't help but be dragged along, somewhat surprised and stumbling at first, but warming to the idea amid all the applause. Anna is frustrated but smiles plastically. The ballet mistress smiles, too, content in a job well done.

*At this point, you might think this is a strange story.  
And you might be wondering when mRNA will show up.  
After all, it is in the title.*



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## *Entracte*

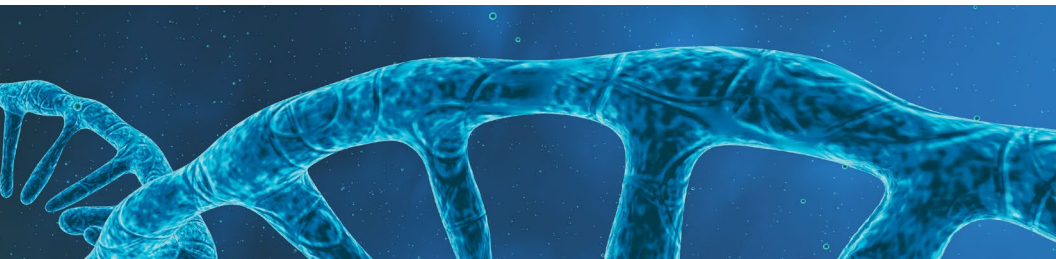
mRNA is a large, fragile molecule. It's made up of smaller bits, called nucleotides, linked together like beads on a chain. Each nucleotide has three parts: a base, a phosphate group, and ribose. The phosphate group from one nucleotide bonds to the ribose from the next, joining the two nucleotides together and creating a link in the mRNA chain. The link itself is called a phosphodiester bond, and it's the reason mRNA is so unstable. It's as if all the beads in the chain are sturdy and nearly unbreakable, but the links between them fall apart at the slightest touch.

## *Pas de deux*

Anna and Mikhail show us how phosphodiester bonds fall apart. In the ballet, Anna plays the lovely phosphate group and Mikhail the sturdy ribose. They belong to two neighboring nucleotides. When Anna and Mikhail hold hands, they form a phosphodiester bond. That bond can be compromised in several ways.

When Anna releases Mikhail's hand and strides downstage, she shows us a type of reaction called phosphodiester bond cleavage. As the name suggests, this reaction breaks the mRNA chain into two shorter pieces. Like a broken necklace, the molecule is ruined and can no longer work as a vaccine.

When Anna pivots from Mikhail's right side to his left, she demonstrates a second, more subtle type of reaction called isomerization. After isomerization, the chain is still intact, but the link is in the wrong place. Isomerization can also compromise the efficacy of the vaccine, but we know less about its effects than those of chain cleavage.



## ACT II: AND mRNA

### *Ode to the ballet mistress*

When the ballet mistress superglues Anna and Mikhail to the chairs, she doesn't stop Anna from moving, but she does slow her down a bit. If she'd been able to slow Anna down even more—maybe using a bigger, heavier chair—it could have taken Anna hours to scoot to Mikhail's left side. By that time, the audience would gotten bored and gone home, and the ballet mistress would have won. This describes what happens when mRNA vaccines are frozen to very cold temperatures. Like a dancer glued to a chair, the mobility of an mRNA molecule is greatly reduced in frozen solids, and reactions happen very, very slowly—too slowly to be of any practical concern. It's not the most elegant solution, but it works. Freezing to ultracold temperatures enabled the first COVID vaccines to reach patients quickly and in an intact form.

For the ballet mistress, the handcuffs were a better idea. They allowed Anna and Mikhail to move about the stage and take their bows but kept them together and in the correct orientation. After the curtain call, the ballet mistress could simply unlock the handcuffs and send Anna and Mikhail on their way. In mRNA, we can make small changes to the chemical structure to prevent degradation in the vial, but that are easily removed once the vaccine is in the body. Like unlocking the handcuffs, this returns mRNA to its native, active form. Modified mRNA molecules like these are called prodrugs; designing them is an active area of research.



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## *Finale*

mRNA has hundreds or even thousands of phosphodiester bonds, not just one. It's like having a thousand Annas and Mikhails, linked together in a very long chain, and capable of pivoting or breaking at any point. Even one misbehaving Anna can ruin the molecule and make the vaccine ineffective.

*Pity the poor ballet mistress responsible for that crowd.*

Scientists are studying mRNA and its degradation with curiosity, imagination, frustration, and persistence. Their efforts have created the COVID vaccines we have today and are paving the way for the new mRNA therapies of tomorrow. They are artists and visionaries, dreamers and designers, architects and poets. And yes, they are ballet mistresses, too.

FINIS

