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INSTITUTE OF CLINICAL RESEARCH

INNOVATION IN EDUCATION

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Transformation in Clinical Trials
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ANNUAL CLINICAL TRIALS SYMPOSIUM

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PIONEERING THE FUTURE OF CANCER TREATMENT: BREAKTHROUGH INSIGHTS AND INNOVATIONS FROM CAR-T ONCOLOGY TRIALS

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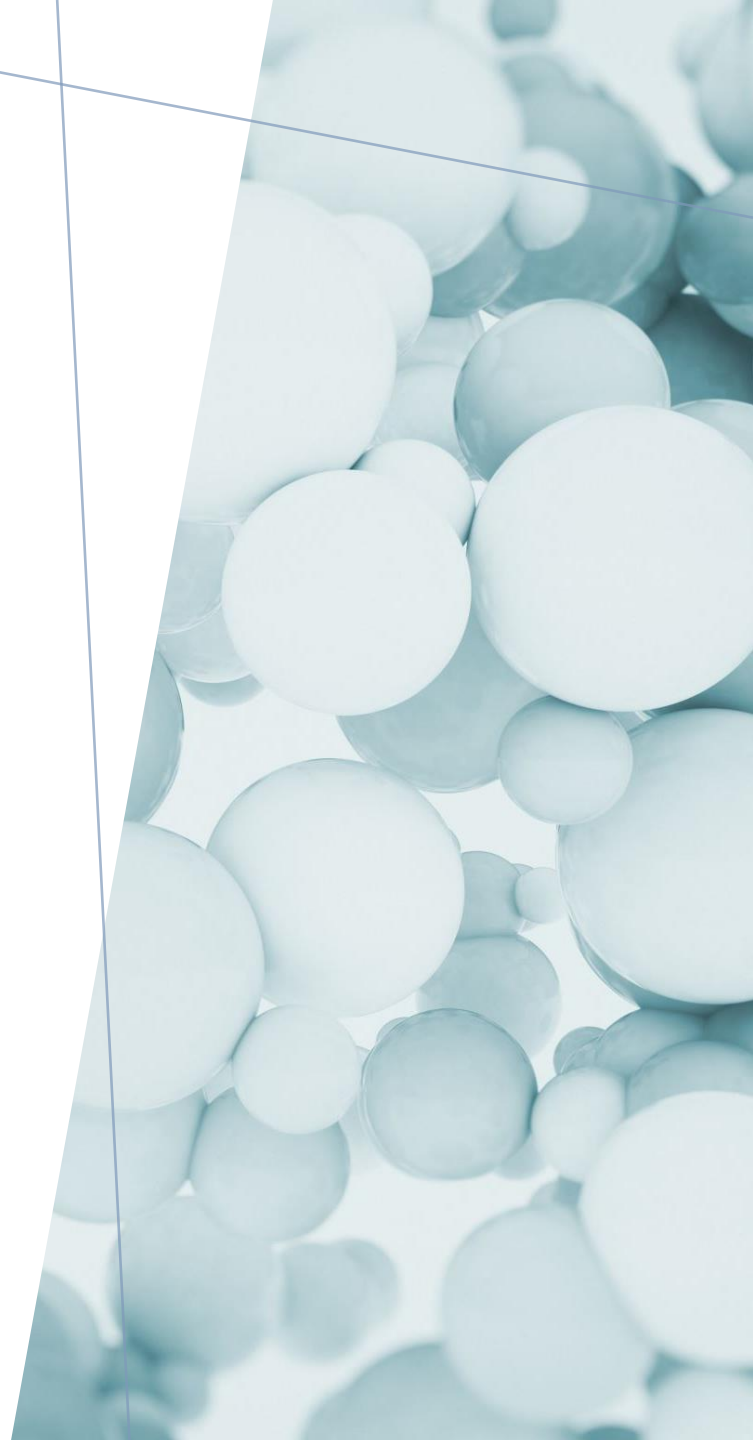
INTRODUCTION TO CAR-T THERAPY AND ITS PROMISE IN ONCOLOGY

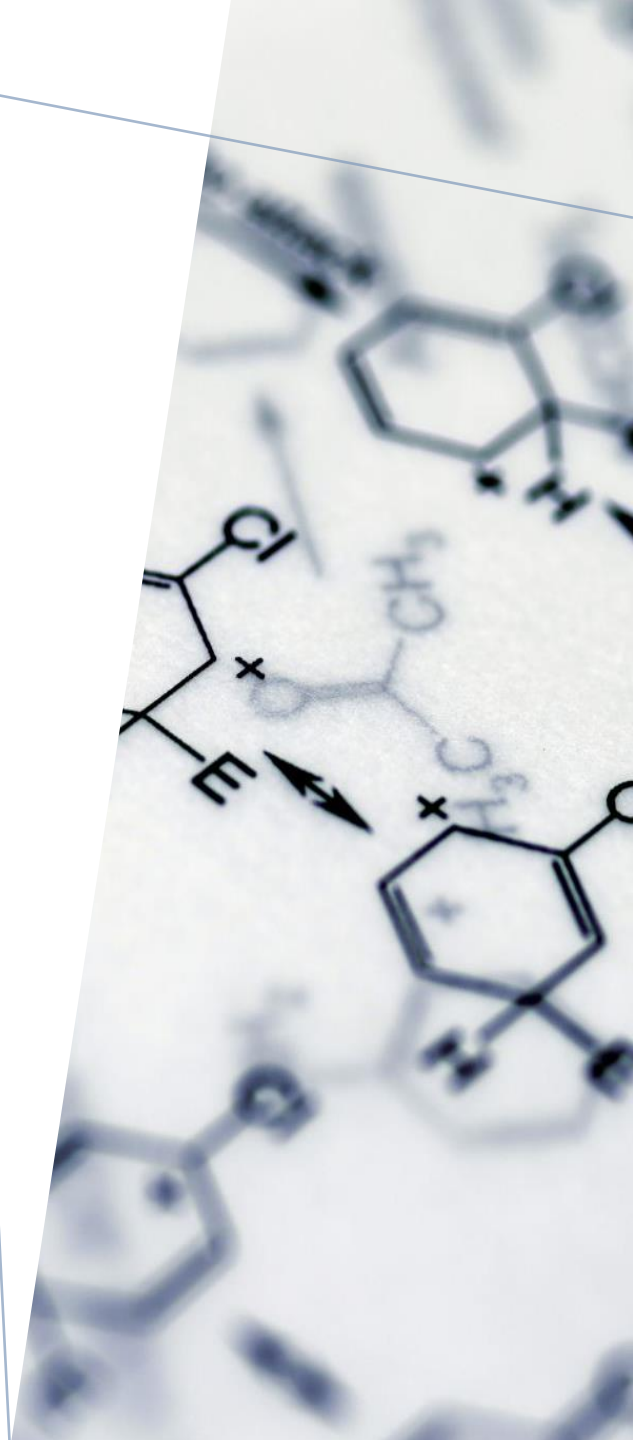


A CUTTING-EDGE IMMUNOTHERAPY THAT USES A PATIENT'S OWN IMMUNE CELLS, GENETICALLY ENGINEERED TO SPECIFICALLY TARGET AND KILL CANCER CELLS.

T CELLS ARE COLLECTED FROM THE PATIENT, MODIFIED TO EXPRESS CHIMERIC ANTIGEN RECEPTORS (CARS), WHICH ENABLE THEM TO RECOGNIZE AND ATTACK SPECIFIC ANTIGENS ON CANCER CELLS, THEN REINFUSED TO FIGHT THE CANCER.

TAILORED TO EACH PATIENT'S SPECIFIC CANCER, CAR-T THERAPY EMBODIES PERSONALIZED MEDICINE, MAXIMIZING EFFICACY BY TARGETING CANCER AT A CELLULAR LEVEL.

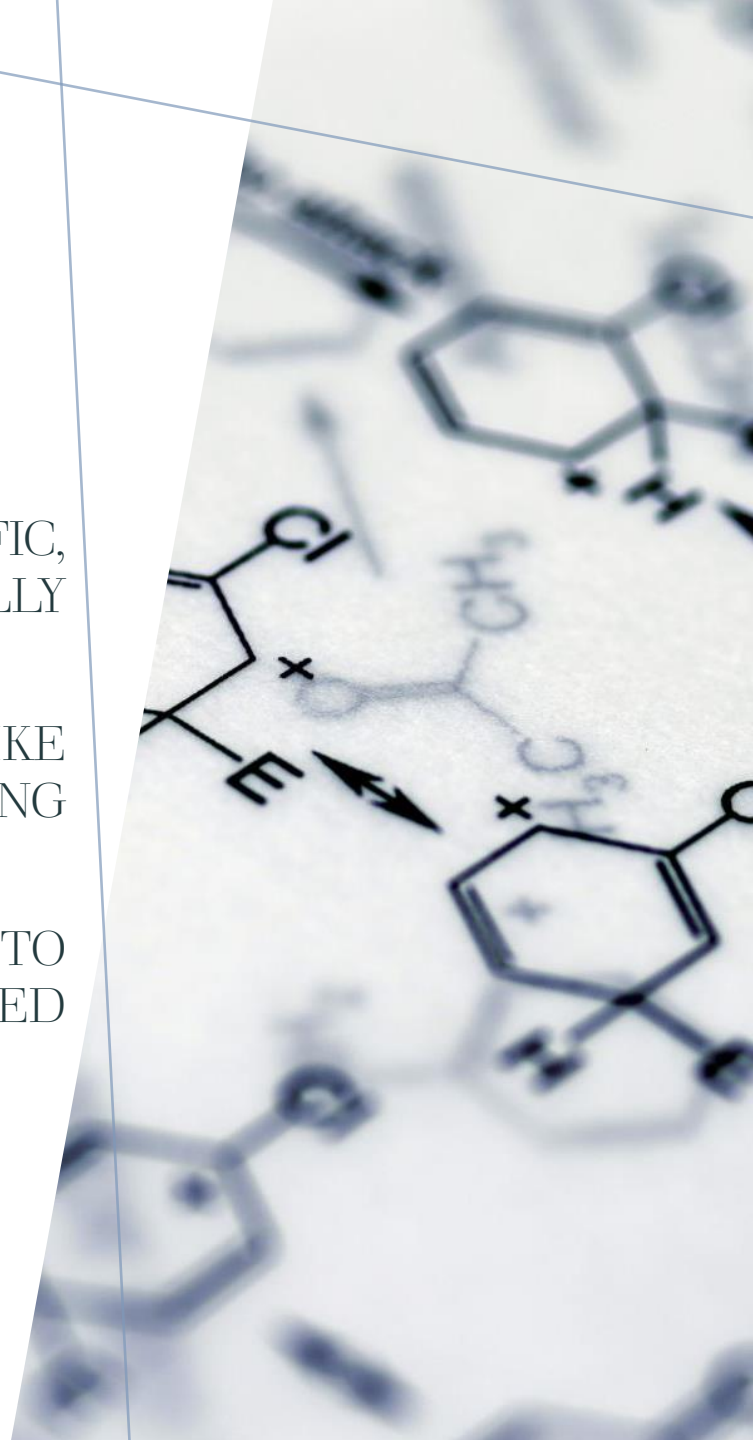
PROVEN HIGHLY EFFECTIVE IN CERTAIN BLOOD CANCERS, SUCH AS LEUKEMIA AND LYMPHOMA, ACHIEVING HIGH REMISSION RATES, ESPECIALLY FOR PATIENTS WHO HAVE NOT RESPONDED TO OTHER TREATMENTS.

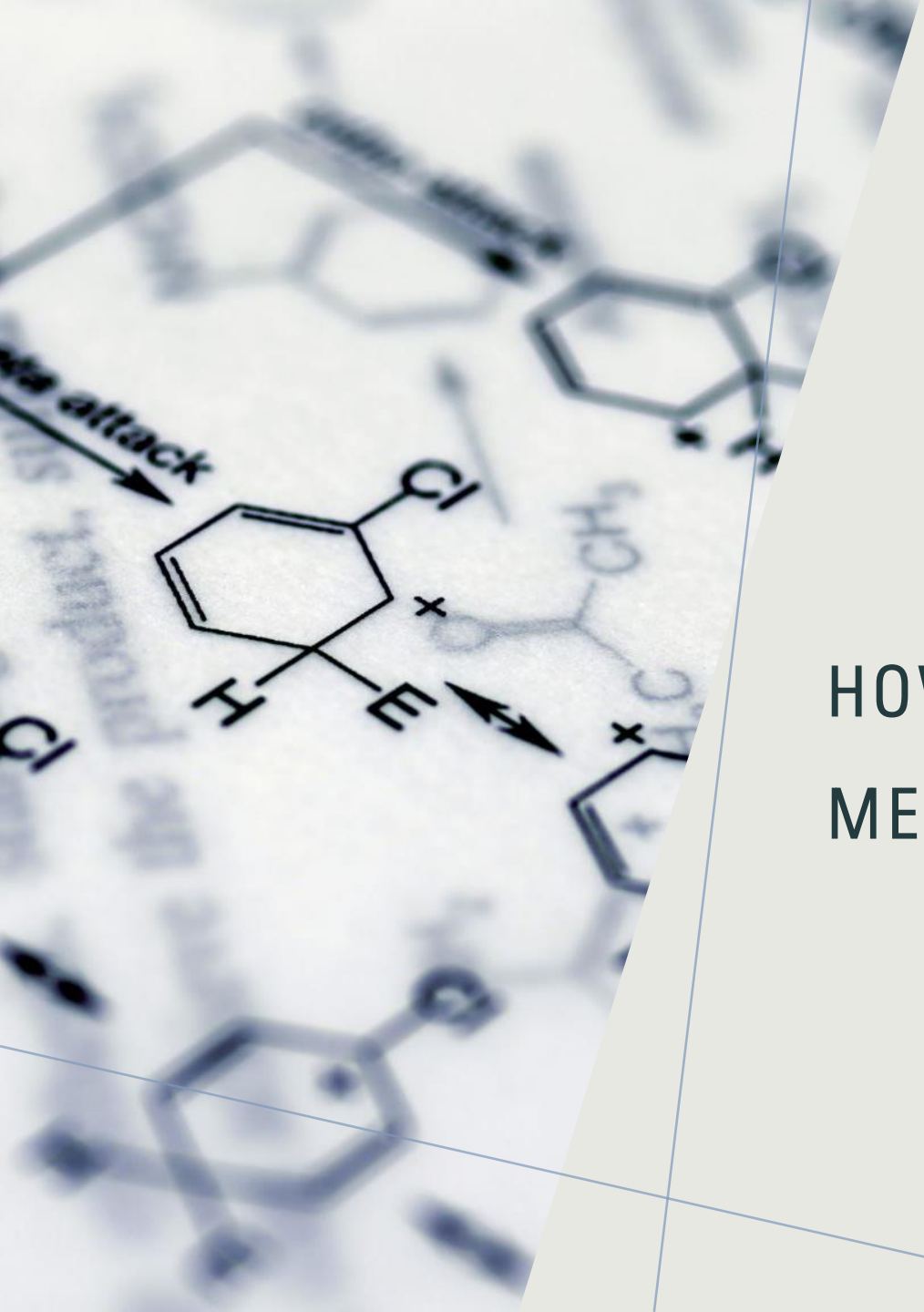


UNLIKE CHEMOTHERAPY OR RADIATION, CAR-T IS TARGETED AND SPECIFIC, REDUCING COLLATERAL DAMAGE TO HEALTHY CELLS AND POTENTIALLY PROVIDING LONG-TERM PROTECTION.

COMPLEX AND COSTLY TO PRODUCE, WITH UNIQUE SIDE EFFECTS LIKE CYTOKINE RELEASE SYNDROME (CRS) AND NEUROTOXICITY, REQUIRING SPECIALIZED MANAGEMENT.

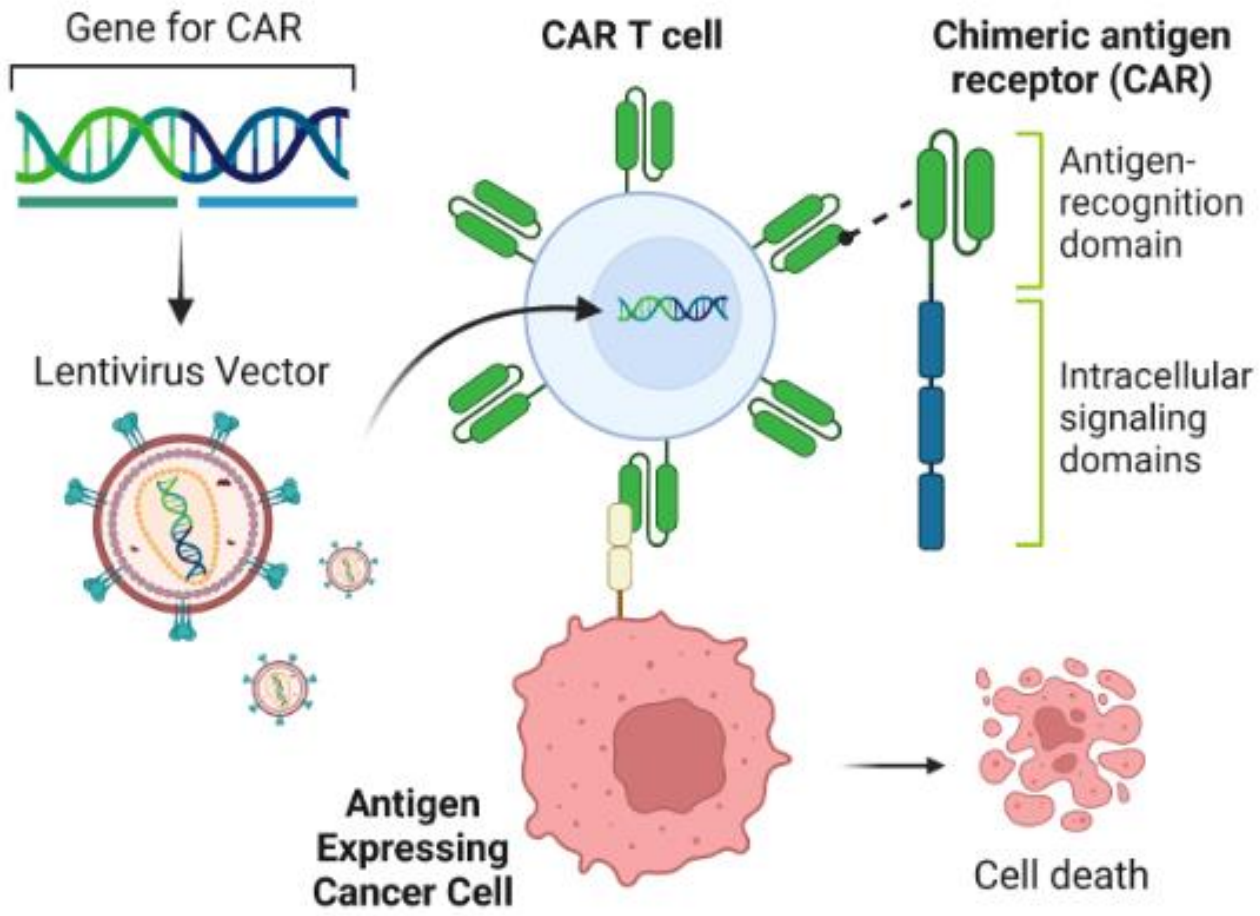
PRIMARILY EFFECTIVE IN BLOOD CANCERS; RESEARCH IS ONGOING TO EXPAND ITS APPLICATION TO SOLID TUMORS AND OVERCOME ASSOCIATED CHALLENGES.



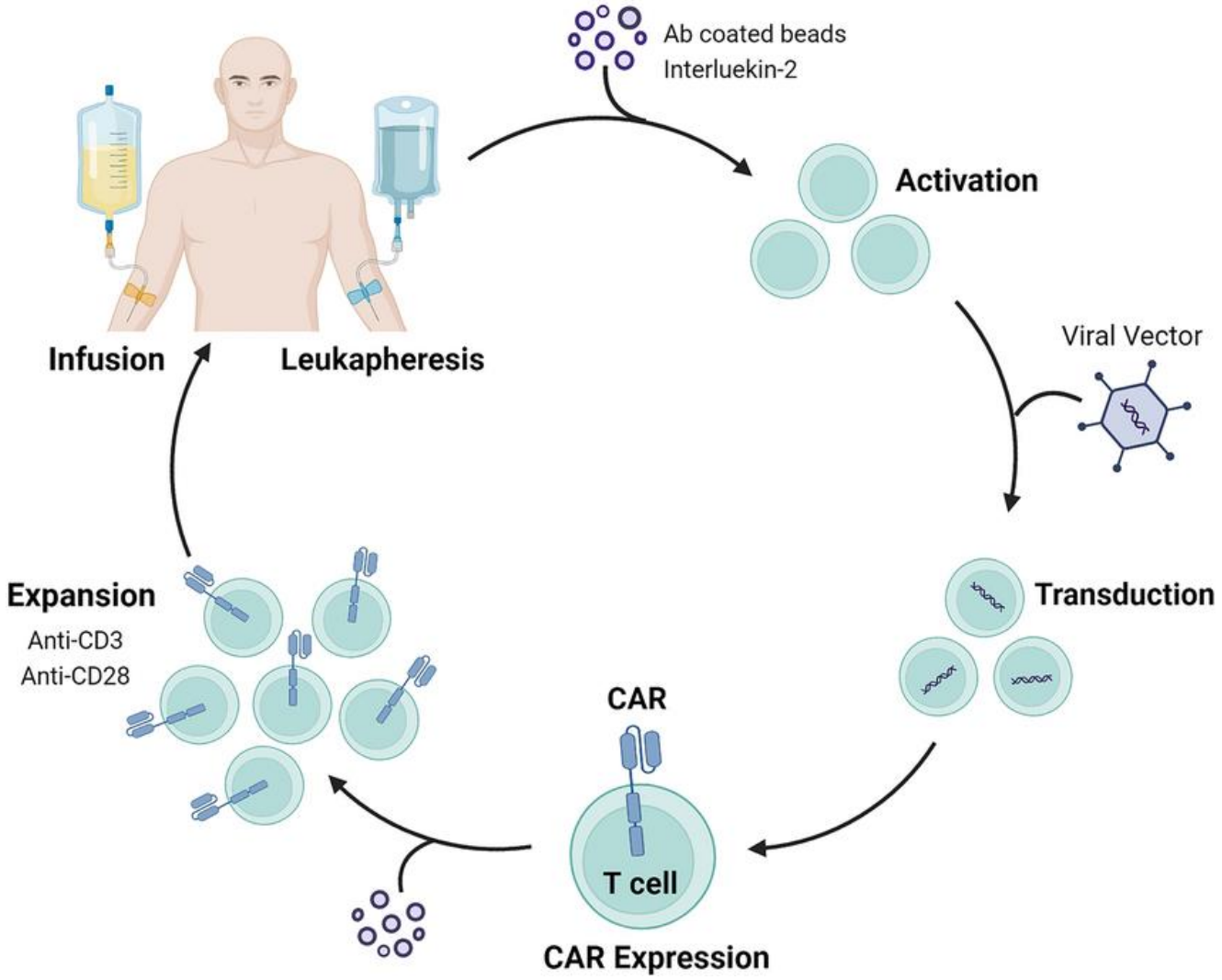


HOW CAR-T CELL THERAPY WORKS: MECHANISM OF ACTION

GENETIC MODIFICATION OF T-CELLS TO TARGET CANCER CELLS

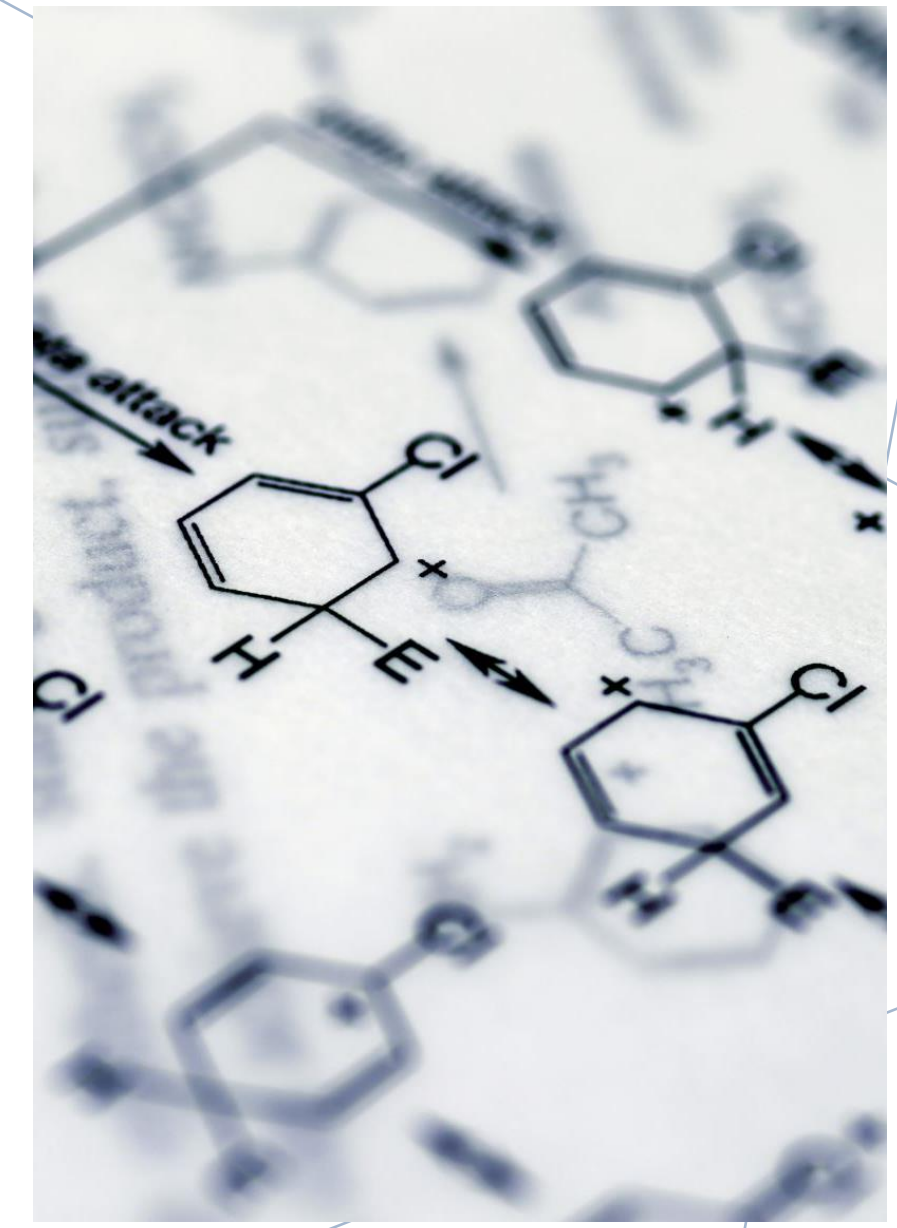


VISUAL REPRESENTATION OF THE CAR-T CELL CREATION AND ACTIVATION PROCESS

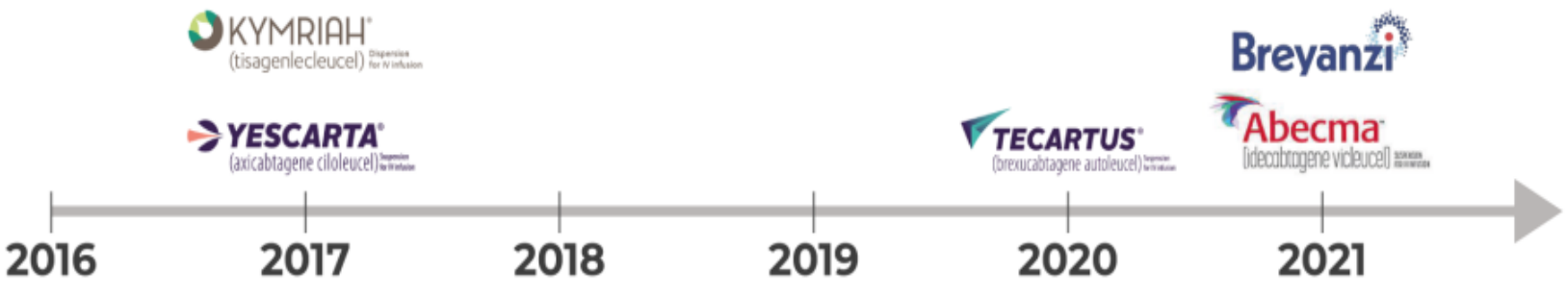


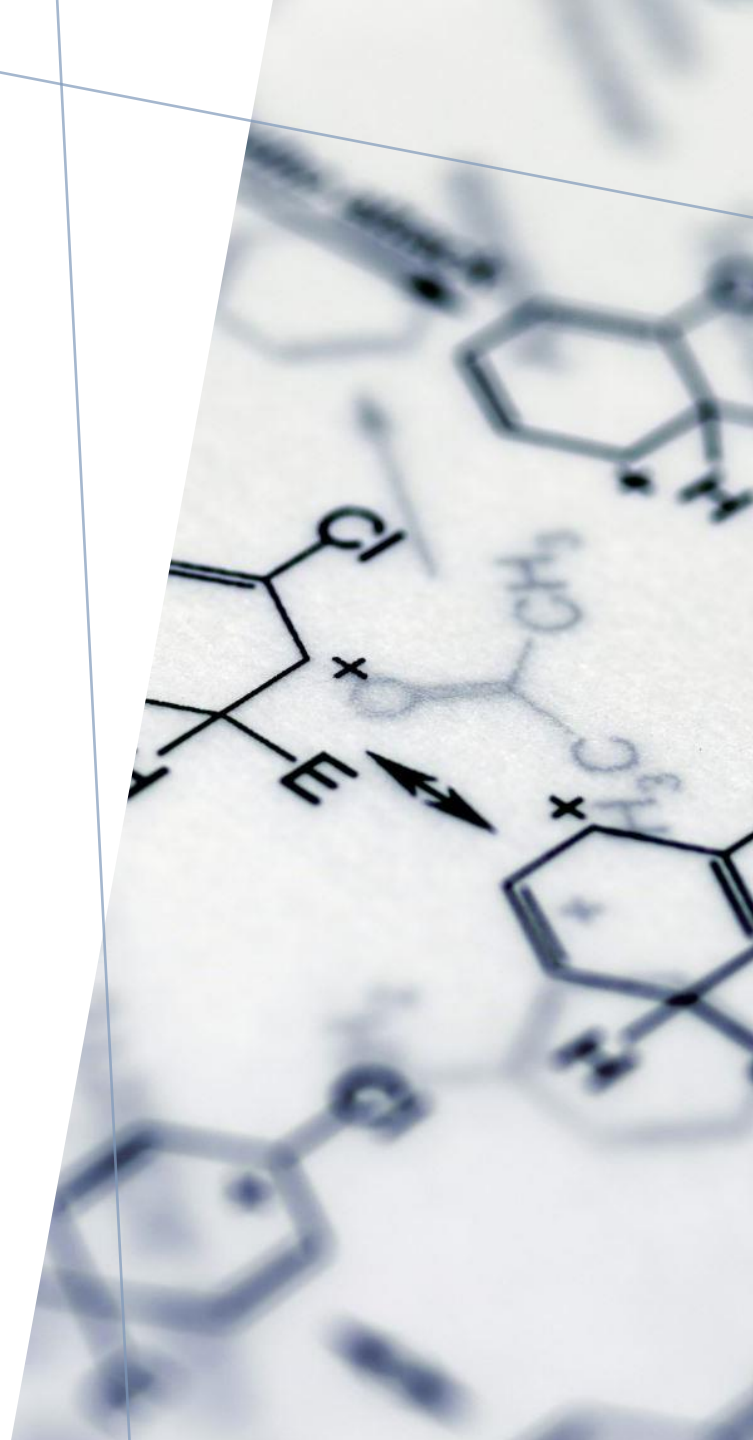
CAR-T THERAPY:

ACHIEVEMENTS AND KEY MILESTONES



FDA approved CAR T-cell therapies





KYMRIAH (2017) & YESCARTA (2018)

FIRST FDA-APPROVED CAR-T THERAPIES, REVOLUTIONIZING TREATMENT FOR CERTAIN BLOOD CANCERS.

KYMRIAH (TISAGENLECLEUCEL)

INDICATIONS: APPROVED FOR PEDIATRIC AND YOUNG ADULT PATIENTS WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND ADULTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL).

TRIAL RESULTS:

RESPONSE RATES: 83% OVERALL REMISSION RATE IN B-CELL ALL.

LONG-TERM SURVIVAL: HIGH RATES OF SUSTAINED REMISSION BEYOND 12 MONTHS.

PATIENT SUCCESS STORY:

EMILY WHITEHEAD'S STORY IS OFTEN CELEBRATED AS A LANDMARK SUCCESS IN CAR-T CELL THERAPY, UNDERSCORING THE TRANSFORMATIVE IMPACT OF KYMRIAH FOR PATIENTS WITH LIMITED TREATMENT OPTIONS. THIS CASE HELPED LEAD TO FDA APPROVAL OF KYMRIAH IN 2017, MAKING IT THE FIRST CAR-T THERAPY APPROVED FOR PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED OR REFRACTORY ALL.

YESCARTA (AXICABTAGENE CILOLEUCEL)

INDICATIONS: APPROVED FOR ADULT PATIENTS WITH LARGE B-CELL LYMPHOMA WHO HAVE NOT RESPONDED TO OTHER TREATMENTS.

TRIAL RESULTS:

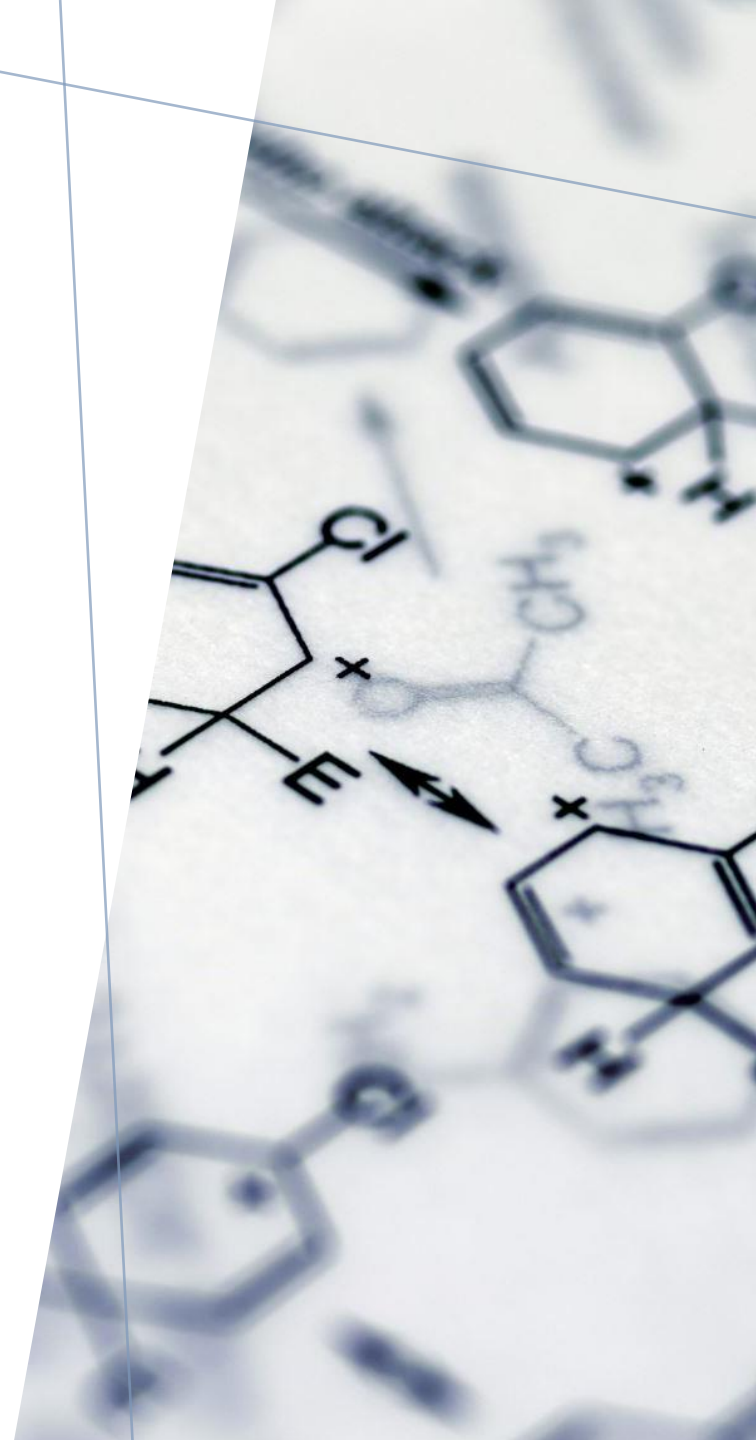
RESPONSE RATES: 82% OVERALL RESPONSE RATE, WITH 54% ACHIEVING COMPLETE REMISSION.

DURABILITY: MEDIAN REMISSION LASTING OVER 6 MONTHS IN CLINICAL TRIALS.

PATIENT SUCCESS STORY:

DOUG OLSON'S STORY IS A POWERFUL EXAMPLE OF HOW YESCARTA HAS GIVEN HOPE TO PATIENTS WITH HARD-TO-TREAT LYMPHOMAS. HIS JOURNEY CONTINUES TO INSPIRE ONGOING RESEARCH INTO CAR-T THERAPIES FOR OTHER CHALLENGING CANCERS, PAVING THE WAY FOR FUTURE BREAKTHROUGHS.

OVERCOMING CHALLENGES
IN SOLID TUMORS WITH CAR-T THERAPY

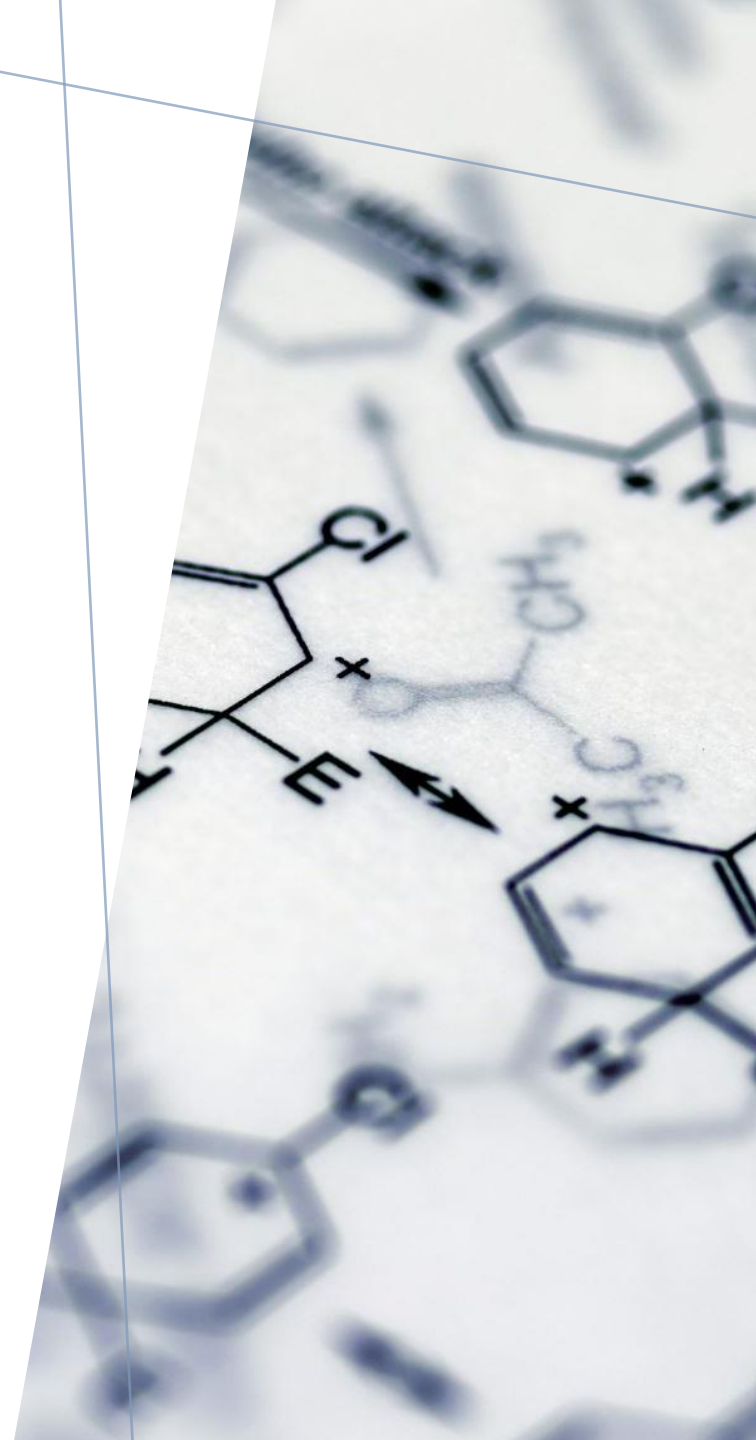


TARGET ANTIGEN SELECTION:

SOLID TUMORS TYPICALLY LACK UNIQUE ANTIGENS FOUND ONLY ON CANCER CELLS, MAKING IT CHALLENGING TO TARGET THEM WITHOUT HARMING HEALTHY TISSUES. RESEARCHERS ARE WORKING TO IDENTIFY CANCER-SPECIFIC ANTIGENS AND ENGINEER CAR-T CELLS THAT CAN DISTINGUISH BETWEEN TUMOR CELLS AND NORMAL CELLS.

OVERCOMING THE TUMOR MICROENVIRONMENT (TME):

SOLID TUMORS ARE SURROUNDED BY A HOSTILE MICROENVIRONMENT THAT SUPPRESSES IMMUNE CELL FUNCTION. THIS INCLUDES IMMUNOSUPPRESSIVE CELLS, CYTOKINES, AND PHYSICAL BARRIERS LIKE DENSE STROMA. SCIENTISTS ARE DEVELOPING CAR-T CELLS WITH ADDITIONAL MODIFICATIONS (E.G., ARMORED CAR-TS) THAT CAN RESIST SUPPRESSION AND FUNCTION EFFECTIVELY WITHIN THE TME.



IMPROVING CAR-T CELL TRAFFICKING AND INFILTRATION:

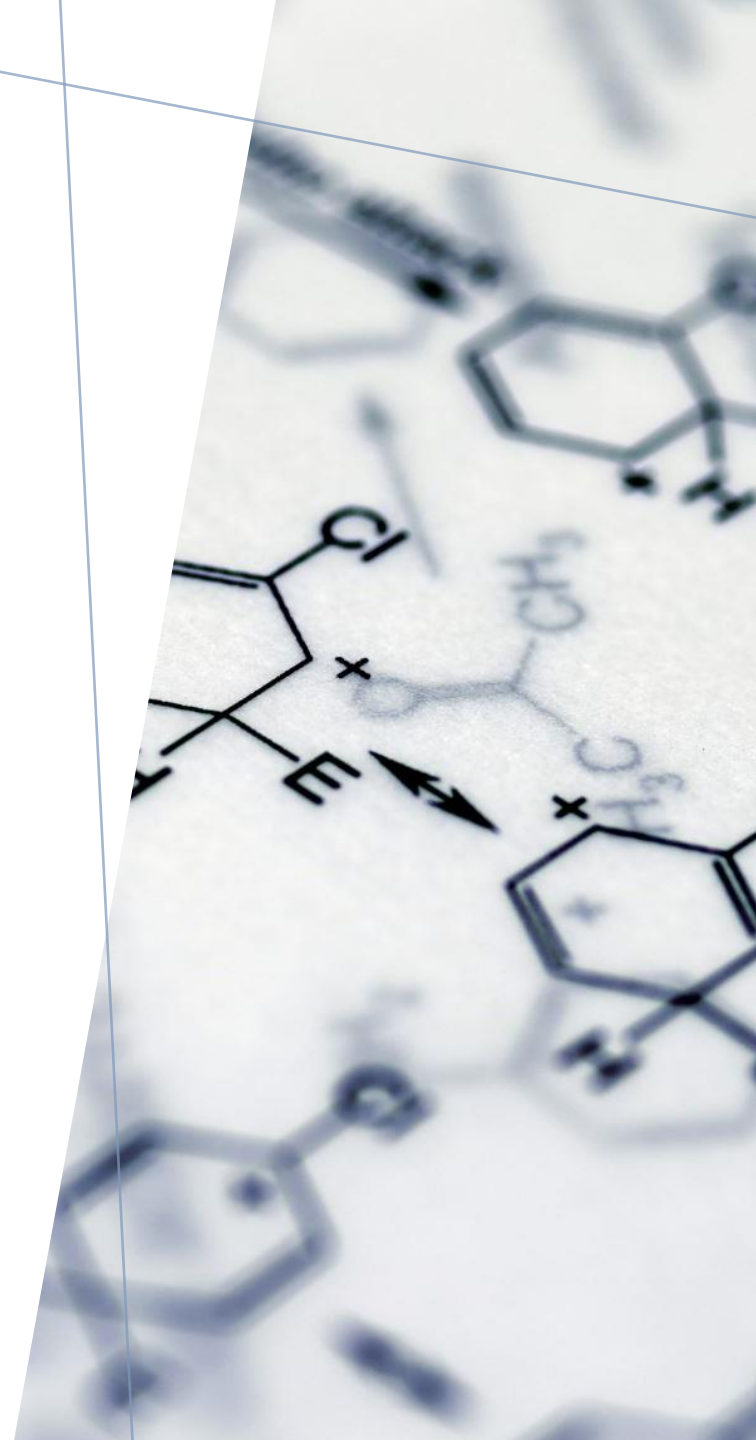
UNLIKE BLOOD CANCERS, SOLID TUMORS ARE OFTEN CHALLENGING FOR CAR-T CELLS TO PENETRATE. STRATEGIES SUCH AS ENGINEERING CAR-T CELLS TO EXPRESS CHEMOKINE RECEPTORS MATCHING THOSE IN THE TME ARE BEING TESTED TO ENHANCE THEIR TRAFFICKING AND INFILTRATION INTO SOLID TUMORS.

ENHANCING CAR-T CELL PERSISTENCE AND DURABILITY:

CAR-T CELLS IN SOLID TUMORS CAN BECOME EXHAUSTED MORE QUICKLY. TO IMPROVE PERSISTENCE, RESEARCHERS ARE INCORPORATING CO-STIMULATORY SIGNALS AND ENGINEERING CAR-TS TO SECRETE SUPPORTIVE CYTOKINES THAT ENHANCE THEIR LONGEVITY AND RESILIENCE WITHIN THE TUMOR.

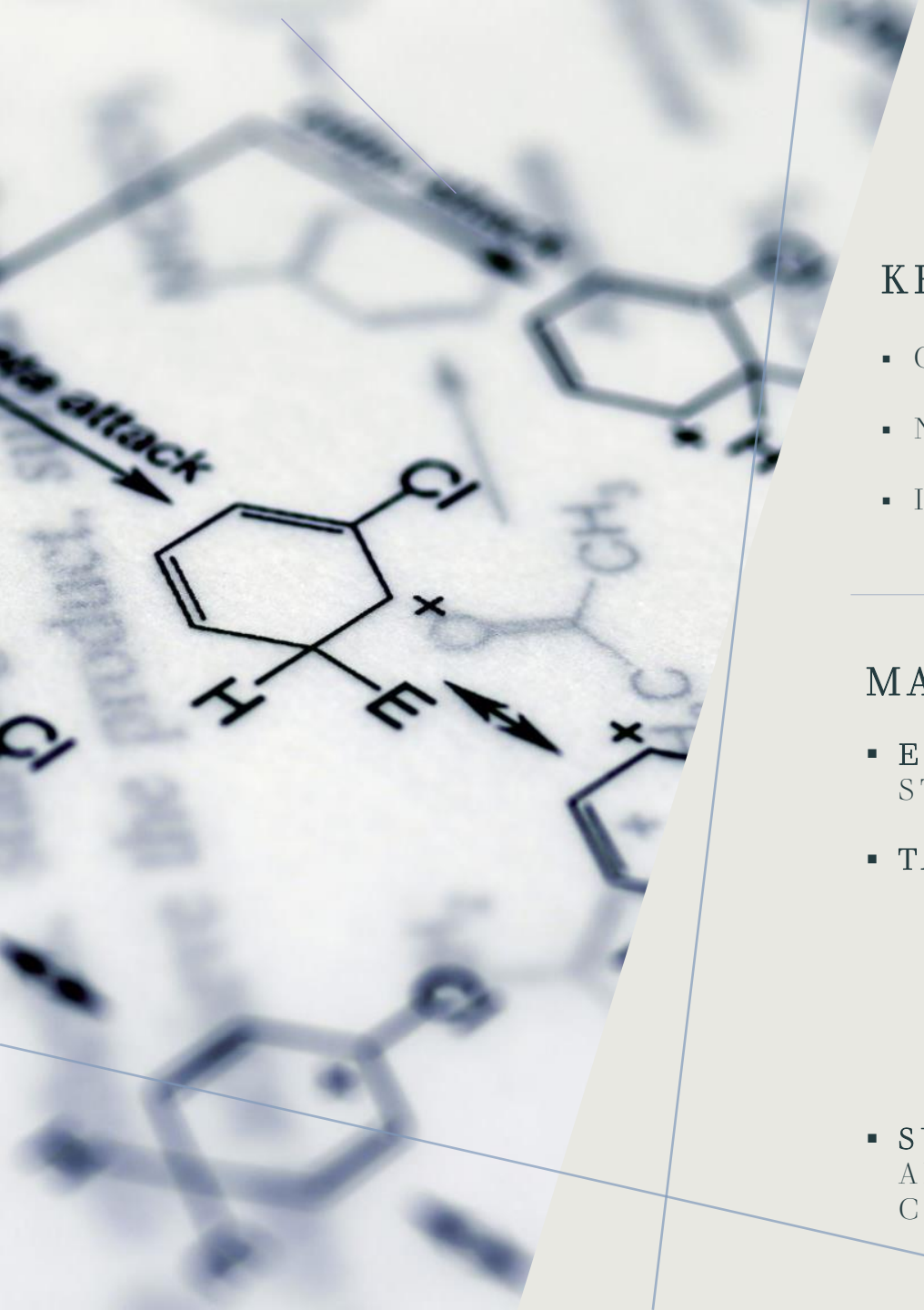
COMBINATION THERAPIES:

COMBINING CAR-T THERAPY WITH CHECKPOINT INHIBITORS, ONCOLYTIC VIRUSES, OR OTHER IMMUNE-MODULATING AGENTS MAY IMPROVE EFFECTIVENESS. THESE COMBINATIONS HELP TO OVERCOME TUMOR DEFENSES, ENHANCE CAR-T FUNCTION, AND IMPROVE TUMOR TARGETING.



SAFETY AND TOXICITY:

MANAGING CAR-T RELATED ADVERSE EVENTS



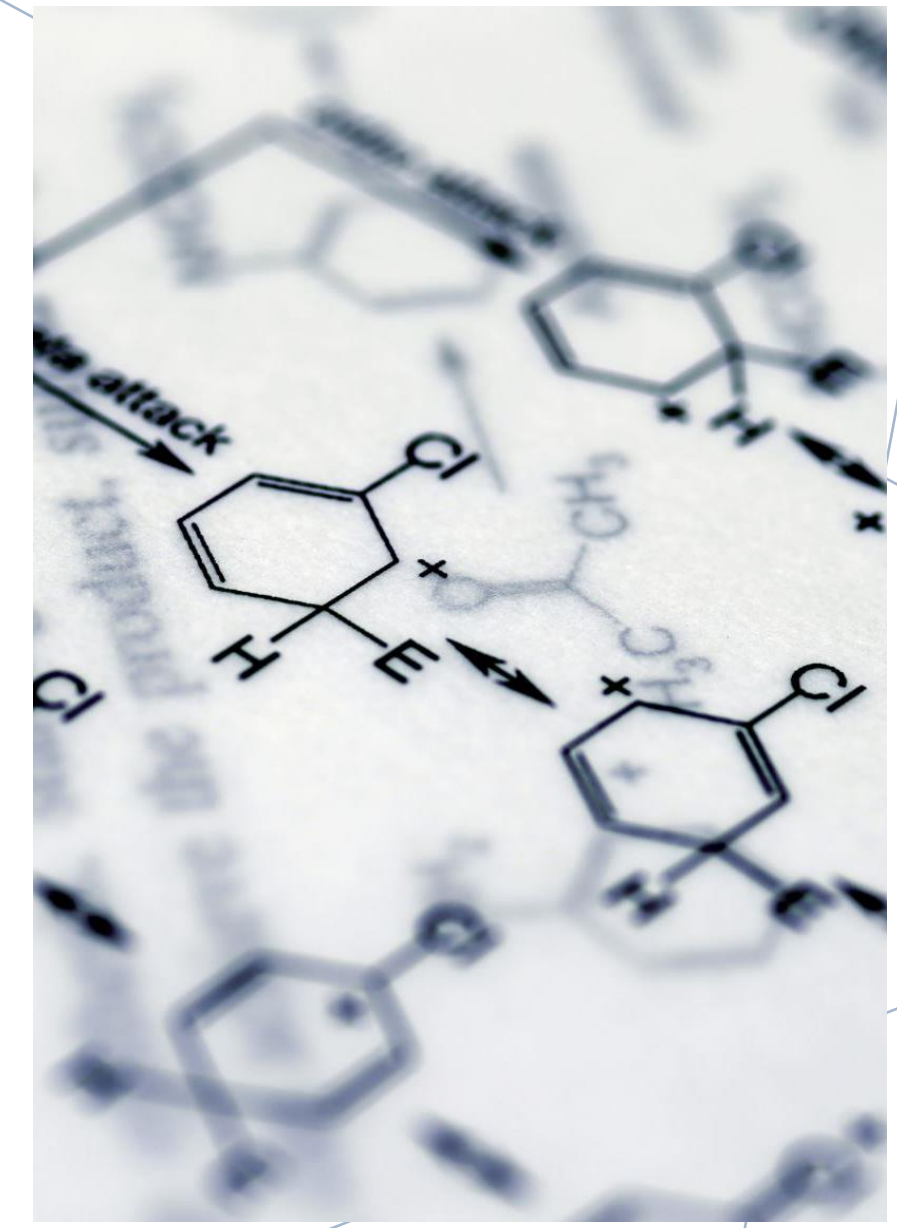
KEY ADVERSE EVENTS IN CAR-T THERAPY:

- CYTOKINE RELEASE SYNDROME (CRS)
- NEUROTOXICITY (ICANS)
- INFECTIONS AND CYTOPENIAS

MANAGEMENT STRATEGIES:

- **EARLY DETECTION**: CLOSE MONITORING POST-INFUSION, USING STANDARDIZED GRADING SCALES FOR CRS AND ICANS.
- **TARGETED THERAPIES:**
  - TOCILIZUMAB & STEROIDS: COMMON FOR TREATING CRS, AS THEY HELP CALM THE IMMUNE RESPONSE WITHOUT IMPACTING CAR-T EFFICACY.
  - ANTI-SEIZURE MEDICATIONS: USED TO MANAGE OR PREVENT NEUROTOXICITY SYMPTOMS.
- **SUPPORTIVE CARE:** ONGOING SUPPORT, INCLUDING ANTIBIOTICS, ANTIVIRALS, AND TRANSFUSIONS FOR INFECTIONS AND CYTOPENIAS.

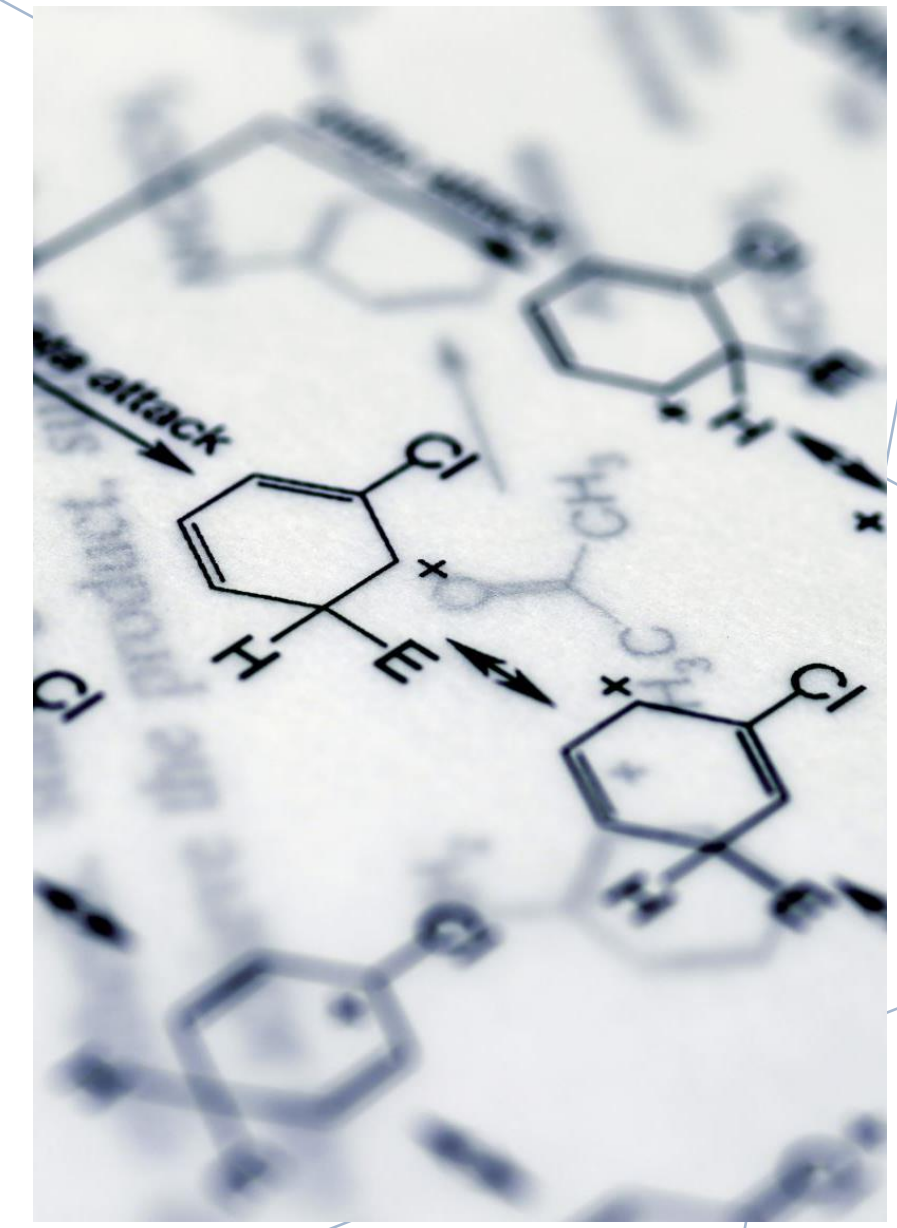
ENHANCING CAR-T EFFICACY AND FUTURE DIRECTIONS



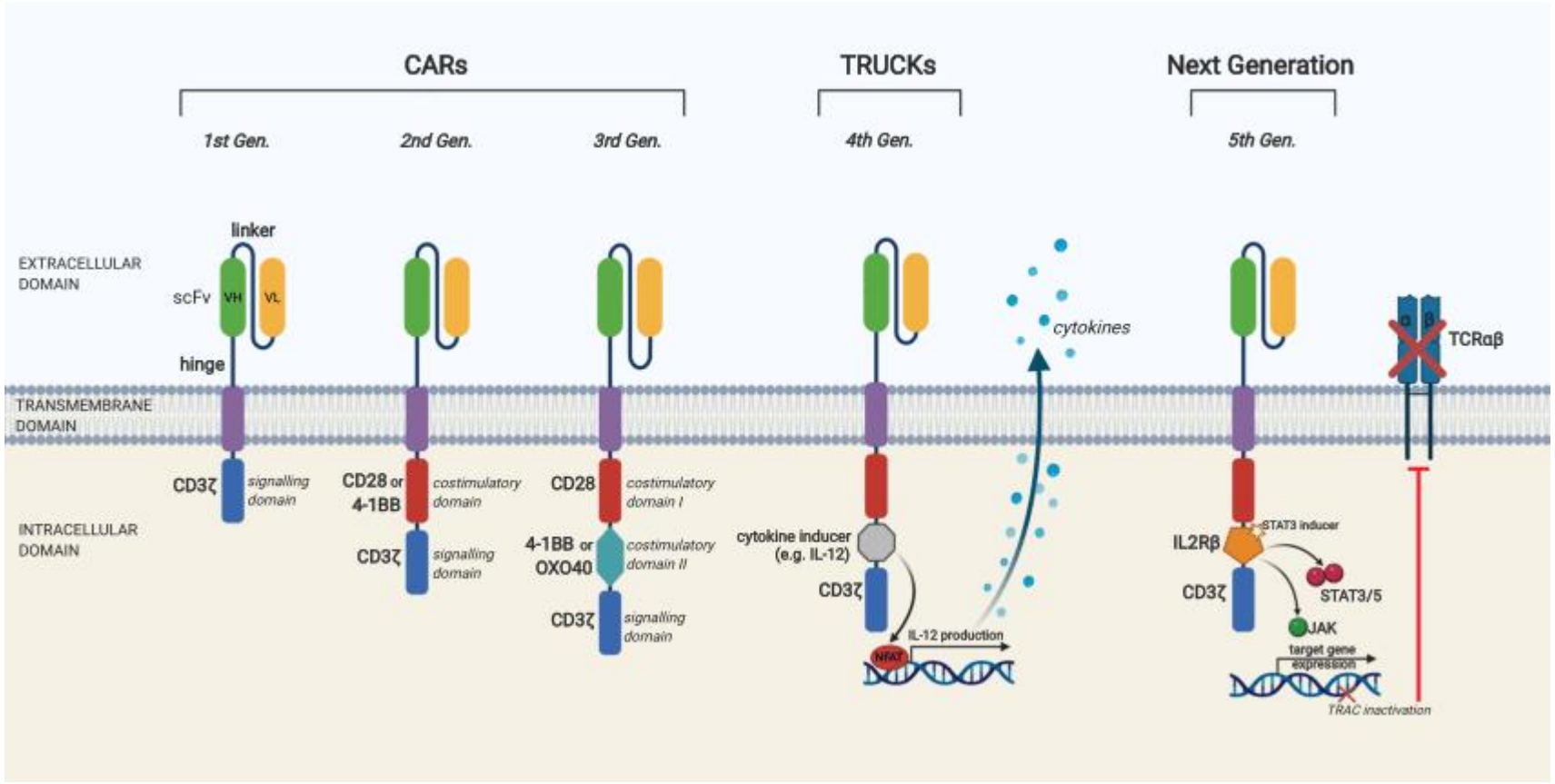
ADVANCES IN CAR DESIGN, SUCH AS DUAL TARGETING CAR-T CELLS AND ARMORED CAR-T CELLS.

COMBINING CAR-T WITH OTHER THERAPIES (E.G., CHECKPOINT INHIBITORS, ONCOLYTIC VIRUSES).

DATA FROM RECENT TRIALS EXPLORING COMBINATION APPROACHES TO ENHANCE RESPONSE RATES.



CAR DESIGN


CARs
TRUCKs
Next Generation
1st Gen.
2nd Gen.
3rd Gen.
4th Gen.
5th Gen.
EXTRACELLULAR DOMAIN
TRANSMEMBRANE DOMAIN
INTRACELLULAR DOMAIN
linker
scFv
VH
VL
hinge
CD3ζ
signalling domain
CD28 or 4-1BB
costimulatory domain
CD3ζ
signalling domain
CD28
costimulatory domain I
4-1BB or OX040
costimulatory domain II
CD3ζ
signalling domain
cytokine inducer (e.g. IL-12)
CD3ζ
cytokines
IL-12 production
NFAT
IL2Rβ
STAT3 inducer
CD3ζ
STAT3/5
JAK
target gene expression
TRAC inactivation
TCRαβ

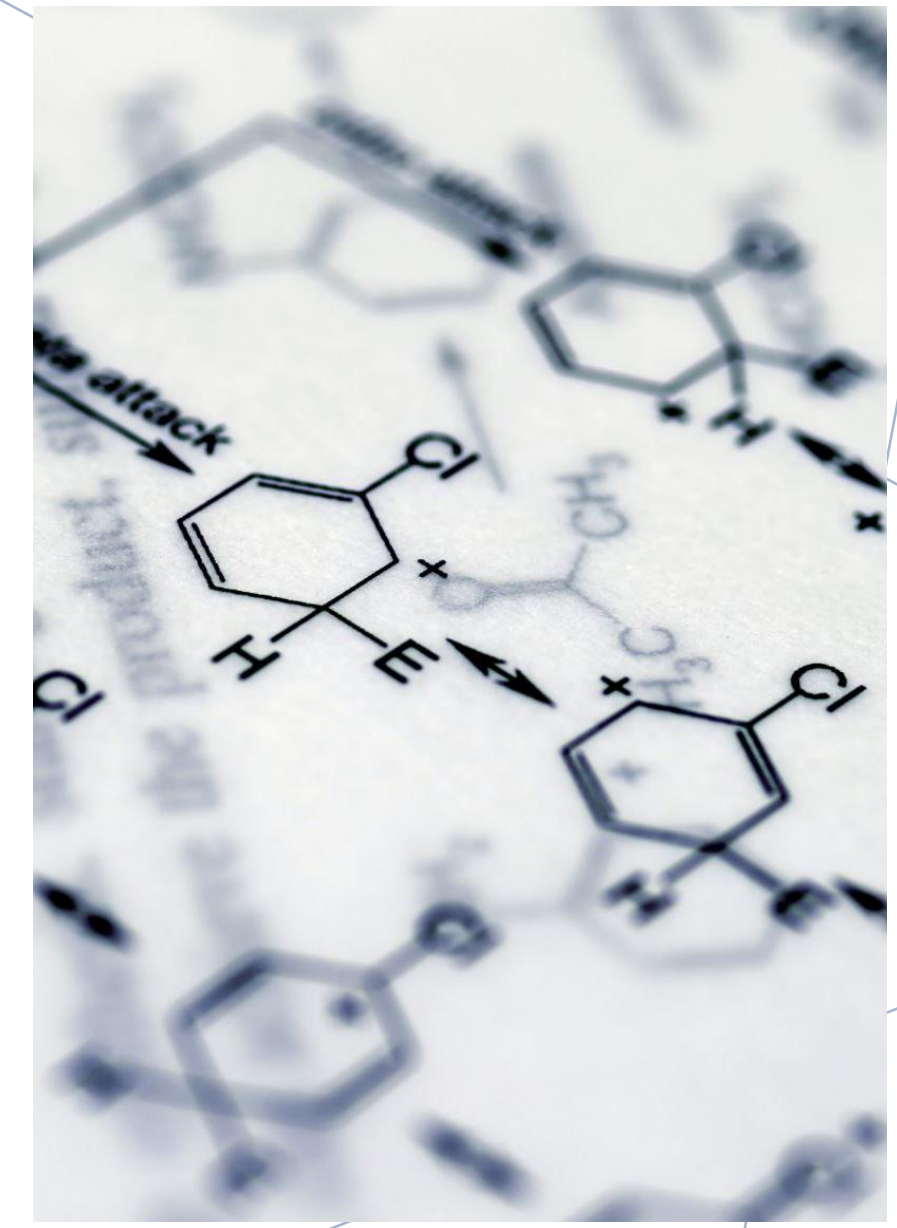
UNIVERSAL CAR-T CELLS: ENGINEERING "OFF-THE-SHELF" CAR-T CELLS FROM HEALTHY DONORS TO REDUCE MANUFACTURING TIME AND COSTS

DUAL-TARGETING CARS: DESIGNING CAR-T CELLS THAT RECOGNIZE MULTIPLE ANTIGENS TO PREVENT ANTIGEN ESCAPE AND TARGET HETEROGENEOUS TUMORS.

SAFETY SWITCHES: INCORPORATING MECHANISMS TO DEACTIVATE CAR-T CELLS IN CASE OF SEVERE SIDE EFFECTS.

ENHANCING SOLID TUMOR TARGETING: OVERCOMING THE IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT AND IDENTIFYING SUITABLE ANTIGENS FOR SOLID CANCERS.

COMBINATION THERAPIES: USING CAR-T CELLS ALONGSIDE OTHER TREATMENTS (E.G., CHECKPOINT INHIBITORS, CYTOKINES) TO ENHANCE EFFICACY.



CONCLUSION: THE ROAD AHEAD FOR CAR-T AND PATIENT-CENTERED INNOVATIONS

CAR-T CELL THERAPY REPRESENTS A GROUNDBREAKING ADVANCEMENT IN CANCER TREATMENT BY HARNESSING AND ENHANCING THE BODY'S IMMUNE SYSTEM TO SPECIFICALLY TARGET AND ELIMINATE CANCER CELLS. THE INTRICATE SCIENCE BEHIND CAR-T INVOLVES GENETIC ENGINEERING, IMMUNOLOGY, AND CELLULAR BIOLOGY, CULMINATING IN A HIGHLY PERSONALIZED AND POTENT THERAPEUTIC MODALITY. WHILE CHALLENGES REMAIN, ONGOING RESEARCH AND INNOVATION CONTINUE TO REFINE CAR-T TECHNOLOGY, PROMISING EVEN GREATER EFFICACY AND BROADER APPLICATIONS IN THE FIGHT AGAINST CANCER

THANK YOU!