ZY-11 – A Specific CD40-siRNA Immune Co-stimulatory Blocker in Autoimmune Disorders and Organ Transplantation

Zyrnat Biotherapeutics

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1. The Company: Zyrnat Biotherapeutics, S.L. (website: zyrnat.com)

- **Established June 2011 as an IDIBELL spin-off**
  - Nephrology Department research group at Bellvitge Hospital-IDIBELL & University of Barcelona laboratories
- **Focused on RNA-interference as ideal post-transcriptional gene-silencing technology platform**
  - Immune-mediated inflammation pathways as key biological targets
    - Co-stimulatory signalling (CD40/CD40L) in Lupus Nephritis and transplant organ Ischemia/Reperfusion injury and Rejection
    - IFNα, STAT4 in Lupus Nephritis
- **US Pharma industry contacts through Cedars Sinai / IDIBELL cooperative agreement**

2. The Product

a) Target indications

I. Lupus Nephritis (LN)

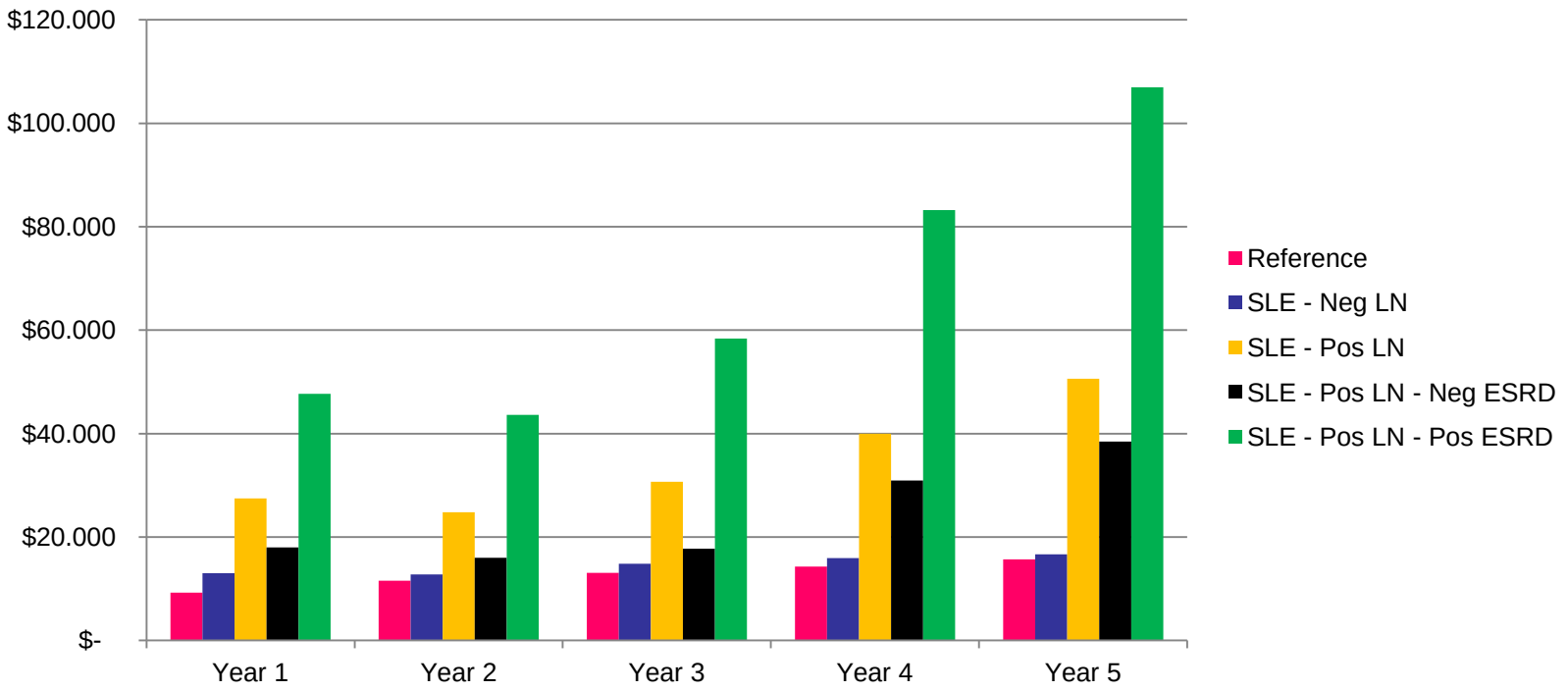
- ZY-11 as effective as cyclophosphamide in preventing proteinuria, histological lesions, immune system activation, and mortality in NZB/W mice with autoimmune nephritis (LN)
- Ready to enter IND/CTA/CTX regulatory GLP studies as no additional pre-clinical efficacy models needed or available for LN
- Potential peak annual sales: $1.5 – 2.2 billion (30% share of $5.0 – 7.5 billion sales for prescription drugs in LN)

II. Prevention of renal transplant rejection and delayed graft function

III. Other immune-mediated forms of glomerulonephritis and autoimmune diseases (RA, MS, Crohn's, etc.)

2. The Product

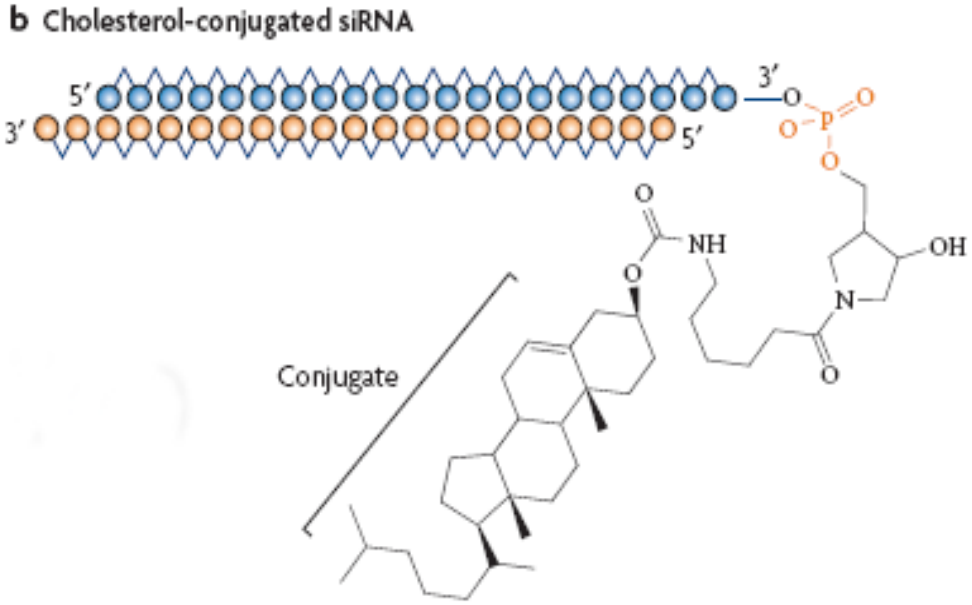
a) Target indications: Lupus Nephritis (LN) – Cost-of-illness



Tracy Li et al., Arthritis & Rheumatism, Vol. 61, No 6, June 15 2009, pp 755-763

2. The Product: ZY-11

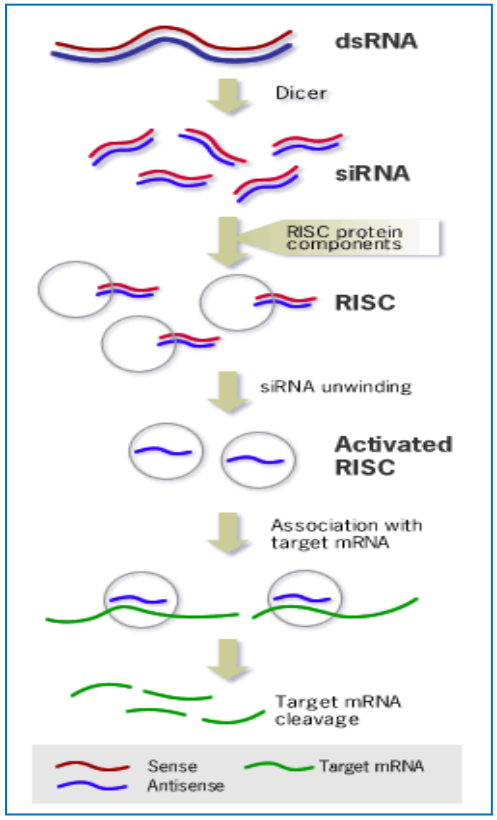
b) Innovative mechanism of action



- **Biological target: human CD40-mRNA**
- **21 nucleotide dsRNA**
- **2 nucleotide overhang 3' anti-sense strand**
- **Chemically stabilized with partial *phosphorothioate* backbone and *2'-O-methyl sugar modification* on the sense and antisense strands**
- **Cholesterol conjugate to the 3' end of the sense strand by means of a pyrrolidine linker**

2. The Product: ZY-11

b) Innovative mechanism of action



Inhibiting mRNA translation is an evolutive defensive process against viruses and other double-stranded RNA (dsRNA) bearing organisms.

Eukaryotic cells recognize extraneous dsRNA from which the RNAse-III-like enzyme **Dicer** generates 20-25 oligonuclotide sequences with dinucleotide 3' overhangs known as small-interfering or small-inhibitory RNAs (siRNAs).

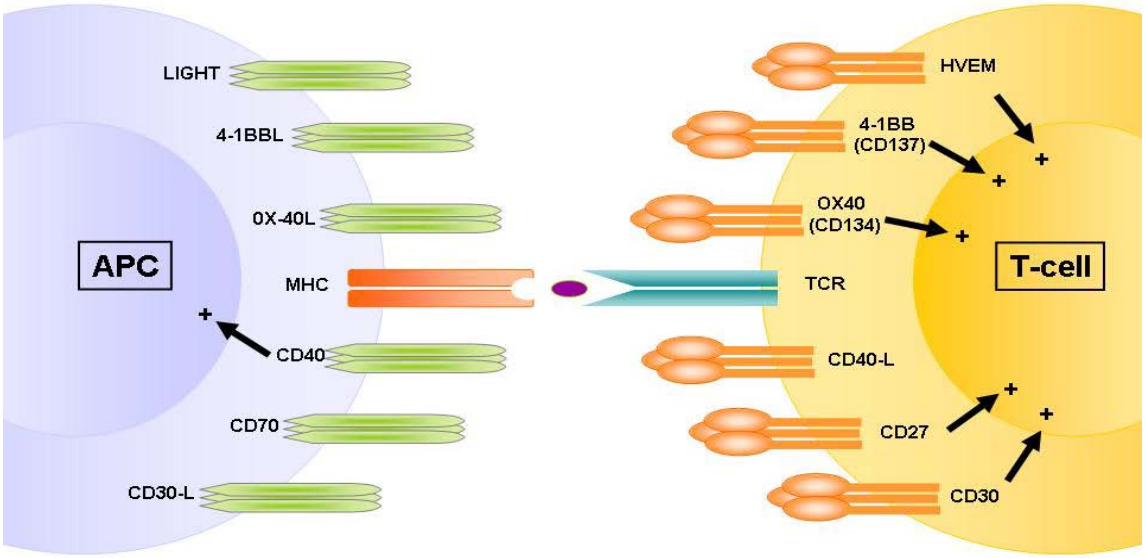
The sense strand attaches itself to endoribonuclease-containing complexes known as *RNA-induced silencing complexes (***RISCs**) which unwind the two strands of the double-stranded siRNA.

The anti-sense strand guides the RISCs towards cognate complementary mRNA molecules which are then cleaved.

Synthetic siRNAs take advantage of this evolutive defensive process to specifically trigger the degradation of target mRNAs.

2. The Product: ZY-11

b) Innovative mechanism of action

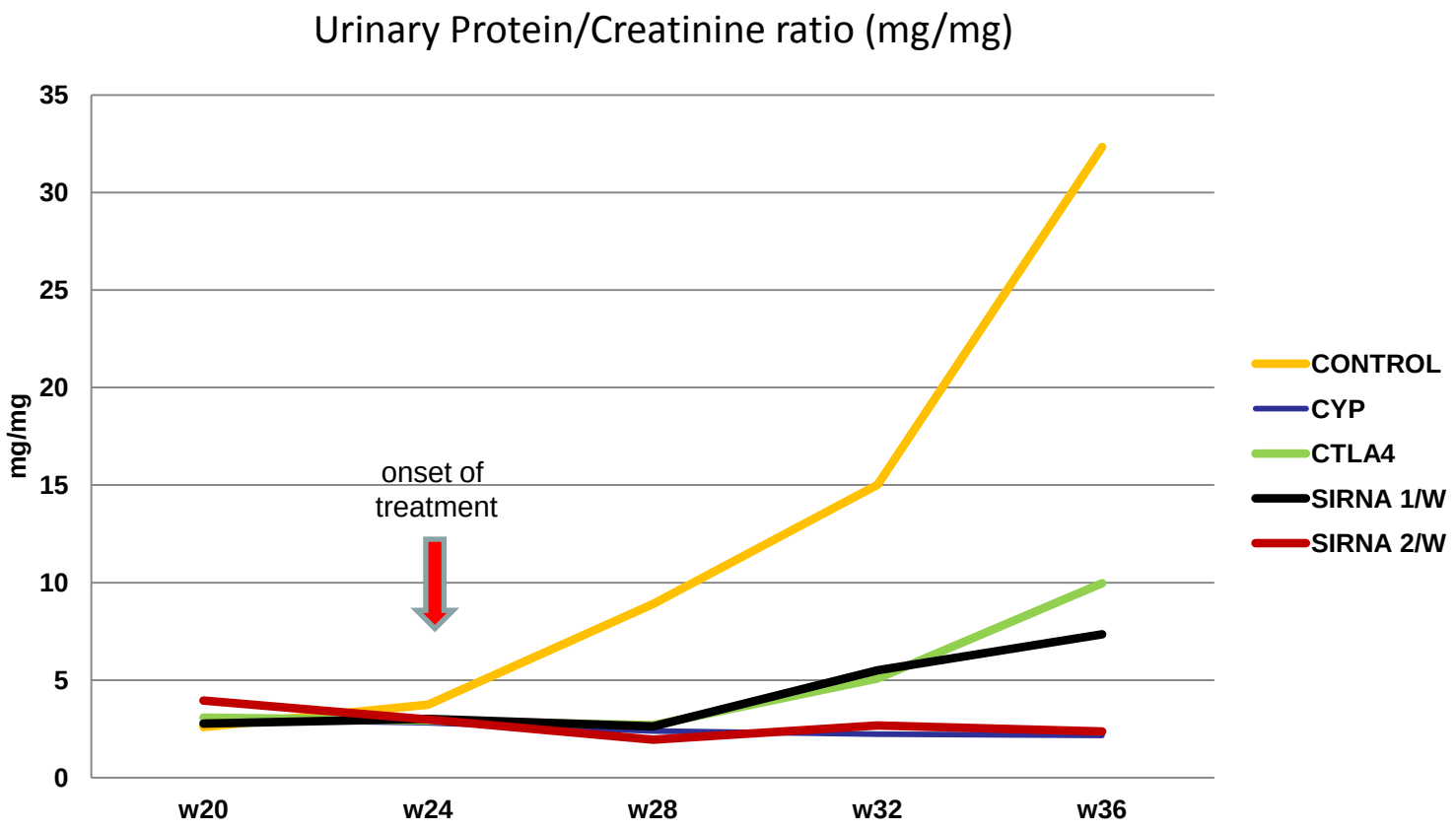


CD40: A tumor necrosis factor 5 (TNFR-5) type-I trans-membrane receptor.

Expressed in:
- ✓ B and T-lymphocytes
- ✓ Antigen Presenting Cells (APCs)
- ✓ Dendritic Cells (DCs)
- ✓ Macrophages
- ✓ Stress-activated renal endothelial and tubular epithelial cells

In the absence of co-stimulatory signals, T-lymphocytes fail to proliferate, or produce cytokines, and become apoptotic.

2. The Product: Effects of ZY-11 on Pr/Cr ratio in NZB/W mice with LN



2. The Product

c) Differential features facing the market

- Currently available non-selective immune-suppressive drugs increase the risk of opportunistic infections, neoplasia, nephrotoxicity, and infertility
- Full-dose **CTLA4-Ig** (abatacept) (anti-CD-28 co-stimulatory pathway) shown to have only sub-optimal efficacy in LN (≈ to low-dose ZY-11)
- **Anti-CD40L** monoclonal Abs effective for renal transplantation and LN but discontinued due to CV toxicity in phase II studies
- **ZY-11** (anti-CD40-CD40L co-stimulatory pathway) has shown efficacy in *in vivo* models of lupus nephritis and renal transplantation
    - Novel and effective immune-modulatory therapeutic opportunities

2. The Product

d) Current status of development

- *In vitro* characterization of ZY-11 and *in vivo* proof-of-principle studies for **LN** in NZB/W mice are complete
  - No additional efficacy *in vivo* models for this indication available
  - Suggested dosing schedule: 2 mg/kg twice weekly
- ZY-11 should enter pre-clinical regulatory GLP studies as quickly as possible with a view to apply for an IND/CTA/CTX seeking authorization to conduct phase I/IIa studies in patients with acutely exacerbated LN as lead indication
  - Safety pharmacology, 'DMPK', toxicology (including non-human primates), and genotoxicity to cover 30-60 day dosing in humans
- IV administration route perfectly acceptable for acute LN indication; SC route desirable/required for long-term maintenance indication(s)

2. The Product

e. IPR protection

- **Zyrnat holds exclusive rights to ZY-11 under patents:**

I. EP 1 614 751 B1

- Valid in 28 countries (ex-USA) (granted Nov 2006)

II. PCT/EP2011/062849

- "TREATMENT OF ACUTE REJECTION IN RENAL TRANSPLANT" (filed Aug 2011)

III. EP 1 138 2286.0

- "STRATEGIES FOR PREVENTION AND/OR TREATMENT OF DISEASES BASED ON CD40 SILENCING" (filed Sep 2011)
  - **Positive opinion from EU review (Lupus nephritis, Renal Ischemia/Reperfusion Injury)**

2. The Product

f. Pitfalls & Risks to be considered

- **Generic risks:**
  - Lack of, or suboptimal efficacy in clinical studies
  - Toxicity (mechanism-based *vs.* unpredictable)
    - Innate immune system activation (not detected so far)
    - Immune-suppression (manageable through dose tailoring)
- **Need for a non-human primate tox study** (≈ $300,000 – $400,000)
- **Relatively high COGs**
  - Common to most or all RNA synthetic compounds

3. Partnering Opportunities

- Given state of readiness of ZY-11 for Lupus Nephritis indication, ideal partner would be medium to large pharma company willing to undertake expedited development path for this indication
  - Estimated critical path to clinical POP ≈ 48 mo
    - 30 – 36 mo for Tox, Safety pharmacology, Genotox to support 30-60 day dosing in the clinic
    - 12 – 18 mo phase I/IIa study: 'Induction of remission of acutely exacerbated Lupus Nephritis' (*de novo* or relapsing)
  - Joint venture ?
  - Technology transfer/acquisition ?