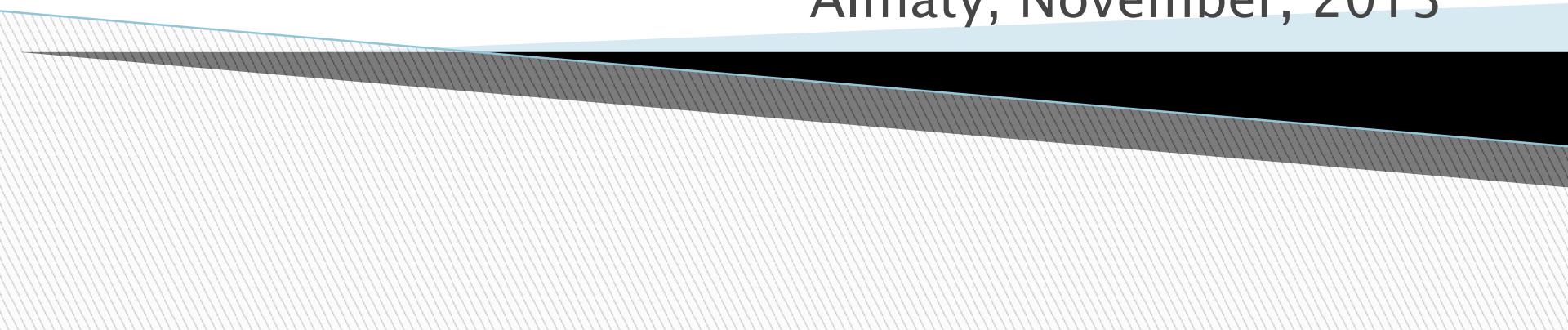


Tuberculosis, Morphology and Physiology

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Tuberculosis

- ❑ Communicable chronic granulomatous disease caused by *Mycobacterium tuberculosis*
- ❑ Usually involves the lungs but may affect any organ or tissue in the body
- ❑ Typically results in caseating granulomas

Routes of infection

□ Respiratory tract

- Most cases are acquired by direct person to person transmission of **airborne** droplets with organisms from an **active case** to a susceptible host

□ Intestinal tract

□ Skin by inoculation

□ Congenital by transplacental spread

Microorganism

▣ **M. tuberculosis hominis**

- Transmitted by inhalation of infective droplets,
- Coughed or sneezed into the air from patients with active “open” Pulmonary TB
- “airborne” or by exposure to contaminated secretions

▣ **M. bovis**

- Transmitted by milk from diseased cows causing intestinal & oropharyngeal TB
- Rare disease for human

▣ **M. avium-intracellulare**

- Very low virulence
- Rarely cause disease in normal hosts
- Cause disseminated infection in 10-30% of AIDS patients

Predisposing Factors

Number of factors predispose to the development of TB

- ▣ **Access of organism**: close contact with open cases of disease, e.g. increased in crowded & unhygienic working and living conditions
- ▣ **Susceptibility of individual**: the old, very young, black & Asian populations have and increased susceptibility

Predisposing Factors

- ▣ **Nutrition**: a disease of the undernourished & under privileged “poor”

- ▣ **Occupation**: increased incidence of TB in some types of pneumoconiosis (silicosis & in health workers)

- ▣ **Other Diseases**:
 - pre-existing chronic lung disease,
 - chronic renal failure,
 - Hodgkin diseases,
 - diabetes mellitus,
 - alcoholism,
 - corticosteroid,
 - immunosuppressive cytotoxic drug therapy
 - Immunodeficiencies including (HIV/AIDS)

Characters of the Organisms

- *Aerobic, acid-fast bacilli*
- Has *no known exotoxins, endotoxins*
- Has waxy coat “high contents of complex lipids” that causes them to retain the red dye when treated with acid in *acid-fast stain* & resist de-colorization

Pathogenesis

- ▣ **Macrophages** are the primary cells infected by *M. tuberculosis*.
- ▣ **Early** in infection, tuberculosis bacilli replicate essentially unchecked, while
- ▣ **Later** in infection, the **T-helper response** stimulates **macrophages** to contain the proliferation of the bacteria.

Pathogenesis

- ▣ *M. tuberculosis* **enters** macrophages by **endocytosis** mediated by several macrophage receptors:
 - **Macrophages mannose receptors**
 - **Complement receptors**
- ▣ Once **inside** the macrophage, *M. tuberculosis* **replicates within the phagosome** by **blocking fusion** of the phagosome & lysosome

Pathogenesis

- The earliest stage of **primary tuberculosis (<3 weeks)** in the nonsensitized individual is characterized by unchecked proliferation of bacteria in the pulmonary alveolar macrophages & airspaces, with resulting **bacteremia** & seeding of multiple sites
- Despite the bacteremia, most patients at this stage are **asymptomatic** or have a mild flulike illness

Pathogenesis

- The **genetic make-up** of the host may influence the course of the disease
- In some people with **polymorphisms in the NRAMP1 gene**, the disease may progress from this point without development of an effective immune response “decreased microbicidal function”
- **NRAMP1 protein** is a **transmembrane protein** found in endosomes and lysosomes & may have role in **generation of anti-microbial oxygen radicals**
- **About 3 weeks** after infection, **a T_H1 response** against *M. tuberculosis* is mounted that activates macrophages to become **bactericidal**

Pathogenesis

- ▣ **T_H0 cells are stimulated by** mycobacterial antigens drained to the lymph node, which are presented with class II major histocompatibility proteins by antigen presenting cells “macrophages”
- ▣ Differentiation of T_H1 cells depends on the presence of **IL-12**,^H which is **produced by antigen presenting cells** that have encountered the mycobacteria
- ▣ Mature T_H1 cells, both in lymph nodes and in the lung, produce **IFN-γ**

Pathogenesis

- ▣ **IFN- γ** is the critical mediator which **activates macrophages to become competent** to contain the M. tuberculosis infection
- ▣ IFN- γ **stimulates formation of the phagolysosomes** in infected macrophages, exposing the bacteria to an inhospitable acidic environment
- ▣
- ▣ IFN- γ **also stimulates inducible nitric oxide synthase (iNOS)**, which **produces nitric oxide (NO)**
- ▣ **NO** generates reactive **nitrogen intermediates** and other **free radicals** capable of **oxidative destruction** of several mycobacterial constituents, from cell wall to DNA

Pathogenesis

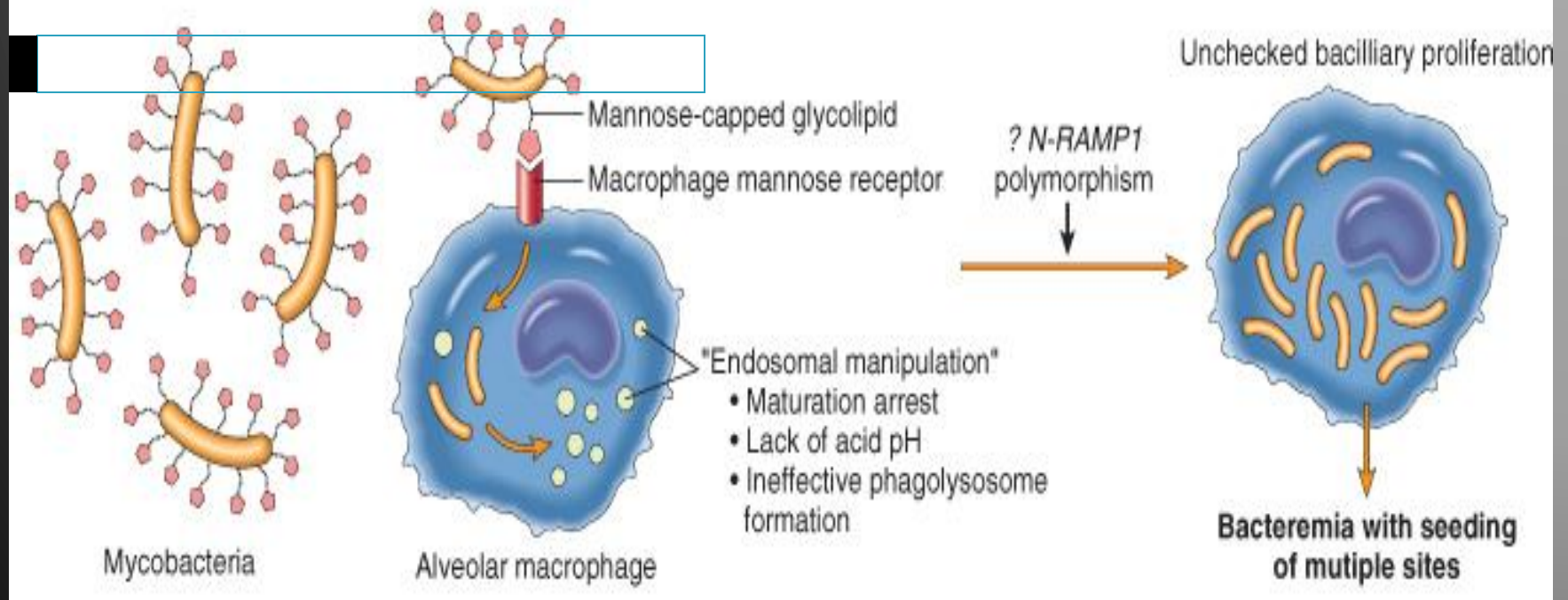
- In addition to stimulating macrophages to kill mycobacteria, the **T_H1 response** orchestrates the **formation of granulomas & caseous necrosis**
- **Activated macrophages**, stimulated by IFN- γ , produce **TNF**, which **recruits monocytes**
- These monocytes **differentiate into the "epithelioid histiocytes"** that characterize the granulomatous response
- **$CD4+ T_H1$ cells** **also facilitates development of $CD8+ T$ cells**, which can kill the TB-infected macrophages
- **Defects** in any of steps of **T_H1 response** result in poorly formed granulomas, absence of resistance, & disease progression

Pathogenesis

- ▣ ***In many people***, this response contains the bacteria and **doesn't cause significant tissue destruction or illness**
- ▣ ***In some people***, the infection progresses and the ongoing immune response **results in tissue destruction** due to caseation and cavitation

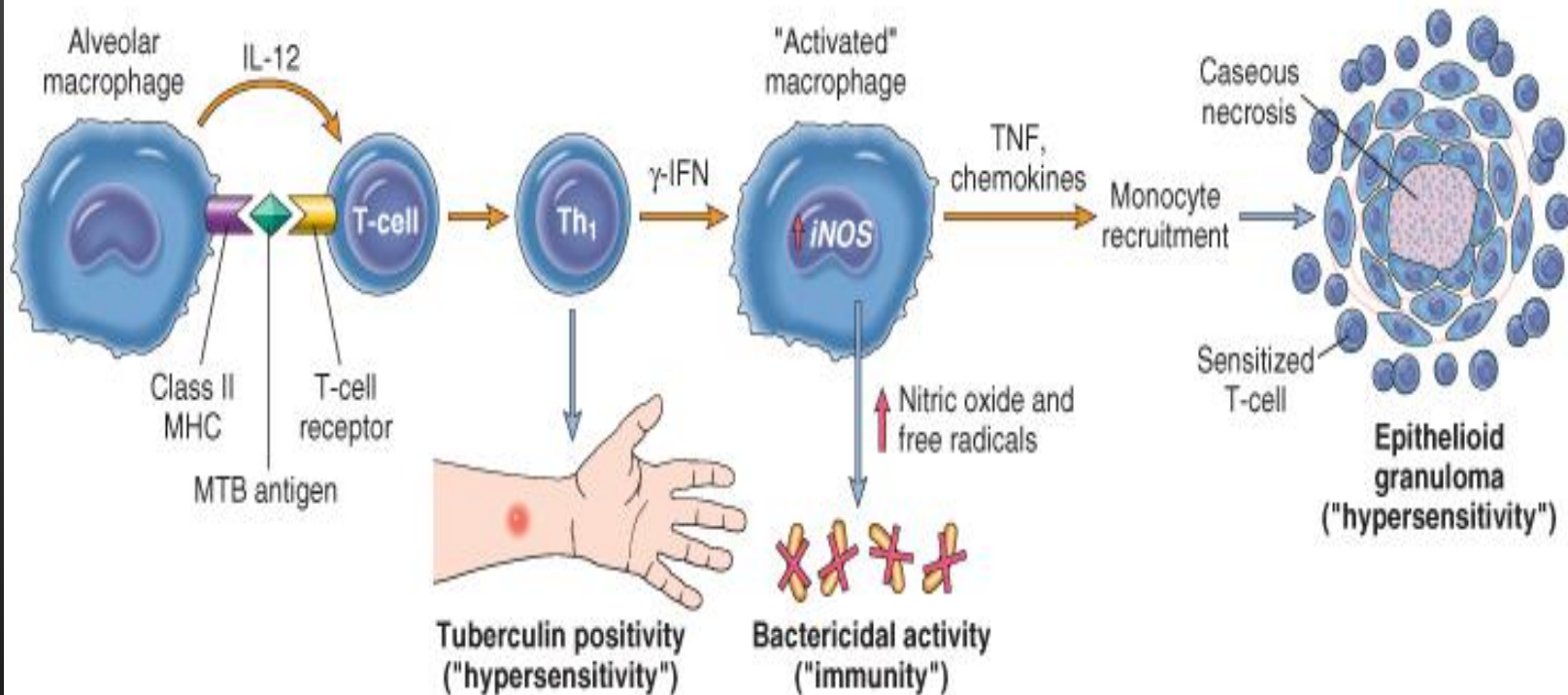
Pathogenesis

A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)



Pathogenesis

B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)



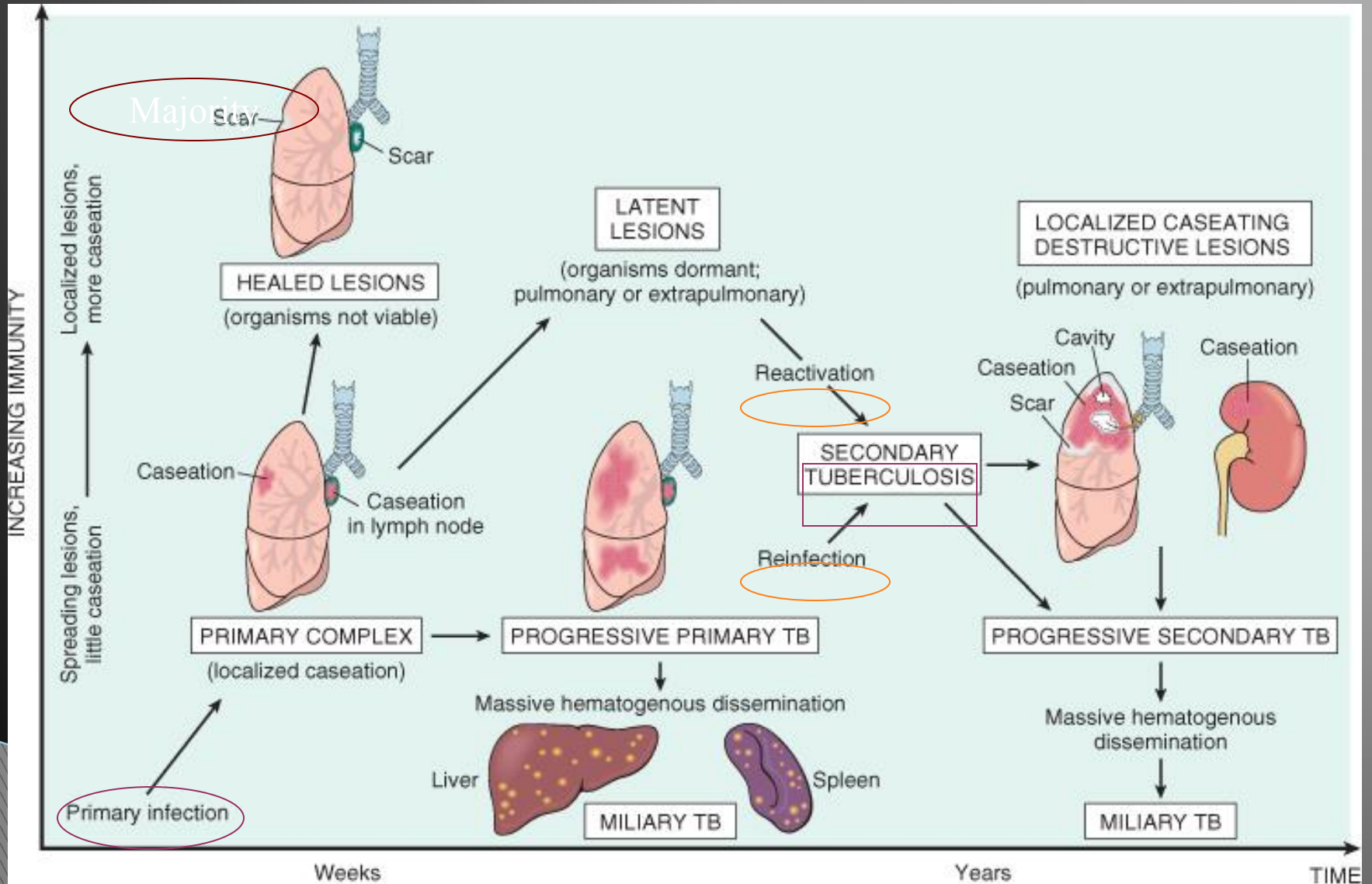
Pathogenesis Summary

- Immunity to *M. tuberculosis* is primarily mediated by **T_H1 cells**, which stimulate macrophages to kill the bacteria
- This **immune** response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction
- **Reactivation** of the infection or **re-exposure** to the bacilli in a previously sensitized host results in **rapid mobilization** of a defensive reaction but also **increased tissue necrosis**

Type IV Hypersensitivity Reaction in TB

- Can be detected by **tuberculin “Mantoux” test**:
 - ~2-4 wks after infection, intracutaneous injection of 0.1 mL of PPD induces a visible & palpable induration “at least 5 mm in diameter” that peaks in 48-72 hrs
 - **Positive test** indicates cell-mediated hypersensitivity & doesn’t differentiate between infection & disease
 - **False-negative test** may be produced by certain viral infections, sarcoidosis, malnutrition, Hodgkin disease, immunosuppression & overwhelming active TB
 - **False-positive test** may result from infection by atypical mycobacteria

TB - Natural History & Spectrum

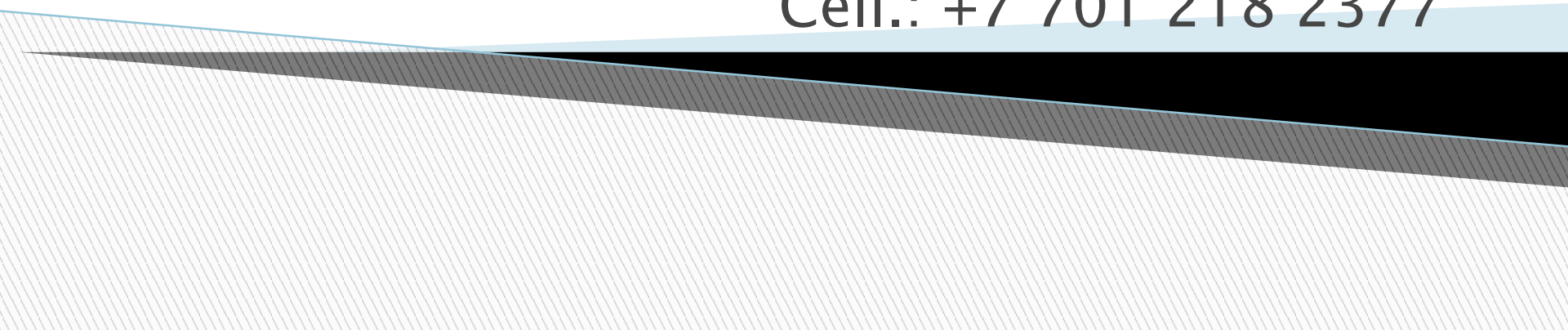


Thanks

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